HRP-503B – BIOMEDICAL RESEARCH PROTOCOL
(2017-1)

Protocol Title: **Smartband/smartphone-based automatic smoking detection and real time mindfulness intervention**

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INSTRUCTIONS
This template is intended to help investigators prepare a protocol that includes all of the necessary information needed by the IRB to determine whether a study meets approval criteria. Read the following instructions before proceeding: 1. Use this protocol template for a PI initiated study that includes direct interactions with research subjects. Additional templates for other types of research protocols are available in the system Library. 2. If a section or question does not apply to your research study, type "Not Applicable" underneath. 3. Once completed, upload your protocol in the "Basic Information" screen in IRES IRB system.

SECTION I: RESEARCH PLAN

1. **Statement of Purpose:** State the scientific aim(s) of the study, or the hypotheses to be tested.

Smoking is the leading cause of preventable disease, disability and death in the US [1]. Although 68% of smokers want to quit, only 7.4% achieve this annually [2], thus more effective treatments are urgently needed. Recent work suggests that mindfulness training may be an effective treatment for smoking by lessening the association between craving and smoking [3-5]. Mindfulness is the practice of paying attention in the present moment, on purpose and nonjudgmentally [6]. Mindfulness training may help smokers learn to pay attention to cravings as they arise and ride them out rather than to react by smoking [7]. An initial clinical trial by our group indicated that mindfulness training reduced smoking rates compared with control [3] and lessened the association between craving and smoking across treatment [8]. More recently, a randomized controlled trial by our group found that mindfulness training was feasible to deliver by smartphone, and smartphone app-based mindfulness training again reduced the association between craving and smoking across treatment [5]. Smartphone-based treatments for smoking have gained popularity due to multiple advantages over in-person treatment, including that apps are more accessible, cost-effective and scalable, and can be used to standardize treatment and as a means for users to track their progress [9]. Moreover, smartphones get treatment into the hand of the user in the real world to intervene in real time [9]. However, existing apps have not thus far exploited their unique potential advantages to aid smoking cessation [10, 11]. Notably, none of the available apps utilize wearable technologies – devices that can be worn on the body and include sensors and an internet connection – to monitor and intervene in smoking. The projected growth of the wearable market [12] implies that apps that exploit this technology would have wide population reach in the near future. Furthermore, all current apps require users to self-report smoking, which depends on one's memory, motivation and other personal and situational factors and can be unreliable [13]. Finally, all existing apps only supply the user with tools to intervene in smoking but do not deliver the intervention contingent upon smoking. The ability to deliver interventions for smoking at the critical moment when craving or smoking occurs may significantly boost efficacy. Therefore, this trial will test the feasibility of using a smartband/smartphone app to detect and track smoking and deliver brief mindfulness exercises to intervene with craving and smoking in real time. This trial tests a three-step intervention to reduce smoking, in which smokers first become aware of their smoking and triggers by tracking smoking; then gain a clear recognition of the actual effects of smoking by "mindful smoking"; and finally learn to work mindfully with cravings rather than smoke. Briefly, daily smokers will wear a smartband to detect and notify them of smoking for 21 days and obtain individual smoking profiles; detected smoking will then trigger a "mindful smoking" exercise for the next 7 days leading up to their quit date at 30 days; after which another mindfulness exercise ("RAIN": recognize, accept, investigate and note cravings rather than smoke) will be delivered prior to each predicted smoking episode according to their individual smoking profile for 30 days post-quit. This study builds on our prior findings that: (1) smoking can be detected by smartband [14]; (2) tracking smoking by smartband reduces smoking [14]; (3) mindfulness exercises are feasible to deliver by smartphone [5] and (4) lessen the association between craving and smoking [3, 5], suggesting a target for treatment. The goals of this feasibility trial are to establish that treatment can be delivered per protocol, participants will adhere to treatment, and treatment will be acceptable, prior to a larger clinical efficacy trial. Feasibility measures are based on guidelines[15] and prior work [16].

Aim 1. To determine treatment fidelity for a smartband/smartphone-based mindfulness intervention. Fidelity measures will be: (1) percent of smoking episodes correctly detected and rate of false alarms; (2) percent of "mindful smoking" exercises correctly triggered by smoking and rate

of false alarms; and (3) users' real time ratings of how timely "RAIN" was delivered to predicted smoking episodes, measured as % of participants and score range (very low, low, moderate, high, very high), with feasibility determined by 75% of participants rating timeliness as moderate or higher. We expect to replicate previous findings of >80% detection and negligible false alarms [14] and to find moderate or higher timeliness ratings. These and other aspects of treatment fidelity will be reported according to recommended guidelines [17].

Aim 2. To determine adherence to a smartband/smartphone-based mindfulness intervention.
Adherence measures will be: (1) percent of time spent wearing the smartband; (2) percent of smoking notifications answered; (3) percent of ecological momentary assessment (EMA) ratings (e.g., timeliness, helpfulness, craving, affect) answered; and (4) percent of mindfulness exercises completed. We expect high response rates based on our earlier studies of smartband-based smoking notifications [14] and EMA of craving and other factors [5]. Adherence cut-offs (e.g., time spent wearing the smartband) will be 80%. Adherence was high in pilot work (90% of participants answered 80% of smoking notifications[14]).

Aim 3. To determine the acceptability of a smartband/smartphone-based mindfulness intervention.
Acceptability measures will be: (1) users' helpfulness ratings after each mindfulness exercise, measured as % of participants and score range (very low, low, moderate, high, very high), with feasibility determined by 75% of participants rating an item as moderate or higher; and (2) from feedback on the User Experiences Questionnaire[15] which includes rating mindfulness exercises (useful, timely, dose, overall timeline); satisfaction (likability, enjoyment, visual appeal, speed, functionality); burden (perceived effort required to participate); intent to continue to use (use or tell friends to use outside of the study); and technology (video, sound, image content, functionality, misuse, suggested improvements). Average responses for a given factor (e.g., satisfaction) on the User Experiences Questionnaire will be tested similarly to ratings, and qualitative analysis of open-ended questions will be used to further evaluate acceptability.

2. Probable Duration of Project: State the expected duration of the project, including all follow-up and data analysis activities.
   5 years

3. Background: Describe the background information that led to the plan for this project. Provide references to support the expectation of obtaining useful scientific data.

A. Significance

The alarmingly high rates of illness and mortality associated with tobacco smoking and the huge financial costs make the reduction of smoking a primary worldwide objective. Despite many years of continued academic and clinical attention to the problem and government investment in large-scale efforts to reduce smoking, the efficacy of clinical interventions for smoking cessation remains surprisingly low [18]. A potentially impactful new way to aid smoking cessation is by providing psychological and behavioral interventions via smartphone apps, which have important advantages that could make them a major player in the efforts to reduce smoking globally [9-11, 19]. While there are presently more than 400 smoking cessation apps on the market, only one has been tested in a controlled pilot efficacy trial [20]. Furthermore, reviews of existing apps report that they have not thus far exploited their unique potential advantages to aid smoking cessation [10, 11]. In particular: **(1)** no available smoking cessation apps utilize wearable technologies; **(2)** all current apps require users to self-report smoking; and **(3)** no available apps deliver real time interventions contingent upon smoking episodes. To address these deficits, this study will test the feasibility of a combined smartband-based

automatic smoking detection and real time smartphone-based mindfulness intervention to reduce smoking.

A.1. Advantages of smartphone-based interventions for smoking

Smartphone-based interventions for smoking and other health behaviors are rapidly gaining popularity due to multiple advantages over in-person treatment. Smartphone-based treatments are more accessible, cost-effective and scalable, treatment can be standardized and users can track their own progress [9]. Smartphone-based interventions additionally offer unique benefits such as providing smokers with direct access to tools for self-management or real time support, and getting treatment into the hand of the user in real world context and potentially just in time [9]. Smartphone use is already an integral part of our daily routine. Smartphone ownership rates are high at 77% of U.S. adults [21], and an estimated 80% among adult smokers motivated to quit [22]. Sixty-two percent of smartphone owners have used their phone in the past year to look up information about a health condition [23]. Sixty-seven percent of mobile phone users check their device for messages, alerts or calls without being prompted by a notification, and 44% of mobile phone users sleep with their phone next to their bed to avoid missing calls, messages or updates [24]. This intensive daily use makes it possible to dramatically increase the number of points of care from the clinic to nearly any time and any place an individual needs support [25]. Such real time support may be especially useful in the treatment of smoking, which is influenced by context-related cues and affective states [26]. Multiple content analyses of smartphone-based treatments for smoking cessation conclude, however, that most available apps only provide simplistic tools such as calculators and manual smoking trackers, and fall short of adhering to clinical practice guidelines [10, 19, 27-30]. Another concern is that smartphone-based interventions for smoking cessation are typically multi-featured apps and it can be difficult to distinguish efficacious components and control for multiple factors in clinical trials. Despite these shortcomings, there is preliminary evidence that smartphone-based treatments can help smokers quit. A recent randomized controlled pilot trial compared smartphone app-based acceptance and commitment therapy with the National Cancer Institute's QuitGuide app (*N*=196), and found that treatment could be effectively delivered by smartphone, and smoking abstinence rates were promising at 13% for the experimental app and 8% for the comparator [20]. Other initial studies support that delivering treatment for smoking by smartphone app is feasible and can reduce smoking [31-35]. This study aims to address the gap between the urgent need to reduce smoking, the dissatisfactory success of current interventions and the limitations of current smoking cessation apps, by testing the feasibility of a smartband/smartphone-based smoking detection and mindfulness intervention.

A.2. Leveraging wearable technology for smoking cessation

A unique feature of mobile technology not yet integrated into available smoking cessation apps is data from wearables. This study will use SmokeBeat (now called SafeBeing), a novel smartband app that utilizes data from wristband sensors to detect the characteristic hand-to-mouth gestures associated with smoking a cigarette and differentiate them from similar hand gestures. Many behavioral treatments for smoking teach smokers to self-monitor their smoking habits including when, where and how often they smoke, in order to learn to identify their smoking patterns and triggers (e.g., "Pack Tracks" in the American Lung Association's Freedom from Smoking program). SmokeBeat advances current tracking methods by automatically monitoring and detecting smoking and notifying smokers of smoking episodes in real time. This feature of SmokeBeat alone was found to reduce smoking as compared to control in a pilot trial [14], a finding consistent with early studies indicating that self-monitoring of smoking behavior alone could reduce smoking [36] particularly among smokers motivated to quit [37]. The ability to accurately track smoking is a critical issue as smokers tend to underestimate or deny smoking [38] and discordance between detected and self-reported smoking rates can negatively impact clinical trials as well as population studies that are used to allocate resources and set health priorities [13]. This study will further utilize SmokeBeat's automatic smoking detection to trigger real time interventions contingent upon detected smoking episodes. No other available smoking cessation app is able to automatically trigger treatment contingent upon smoking. Finally, SmokeBeat uses a backend

platform for storage and analysis of big data from wristband sensors and applies machine learning techniques to these data to generate individualized profiles of smoking behavior, for example the average times each day of smoking episodes. Individual differences in smoking behavior in daily smokers can be characterized by regular patterns of smoking frequency [39] driven by nicotine dependence and other affective and situational factors [40, 41]. This trial will use SmokeBeat to track smoking and characterize individualized smoking profiles in order to deliver real time interventions targeted to predicted smoking episodes. Overall, this study will use SmokeBeat (now called SafeBeing) to: (1) automatically monitor and detect smoking, (2) deliver real time interventions triggered by smoking episodes and (3) deliver treatment targeted to predicted smoking episodes according to individualized smoking profiles.

A.3. Mindfulness interventions for smoking cessation

This trial combines smartband and smartphone technology to deliver brief mindfulness interventions for smoking. Mindfulness has been defined as the awareness that arises when paying attention in the present moment, on purpose and nonjudgmentally [6]. Mindfulness has been operationalized in research to include: (1) maintaining attention on one's immediate experience and (2) cultivating an attitude of acceptance or nonjudgement toward one's experience [42]. Mindfulness training typically involves the practice of attention regulation, body awareness and emotion regulation [43]. A growing body of evidence supports testing mindfulness training for the treatment of substance use disorders. Recent reviews report that mindfulness-based interventions are associated with reduced consumption of substances of abuse as compared with several active and inactive control groups [44-46]. Furthermore, in several studies, mindfulness training led to reduced craving and increased mindfulness, suggesting a potential mechanism for clinical outcomes. Limitations of these studies were also identified, including small sample sizes and lack of reported methodological details [47]. Nevertheless, overall findings suggest that mindfulness training may be an effective treatment for addictions including smoking. For smoking cessation, mindfulness training may help smokers learn to work mindfully with cues, cravings and affective states that trigger smoking. Smokers learn to become aware of cues and triggers and pay attention to cravings as they arise, and to accept their experience and learn to ride out the cravings rather than to react by smoking [7]. Specifically, mindfulness training has shown utility in reducing cigarette craving and withdrawal [48, 49], aiding in smoking cessation [3, 50] and in supporting recovery from lapses following a quit attempt [51]. A clinical trial by our research group randomized subjects (N=88) to mindfulness training or the American Lung Association's Freedom from Smoking program [3]. Intent-to-treat analysis indicated that participants randomized to mindfulness training had a significantly greater reduction in smoking post-treatment that was maintained at 4-months follow-up (F=11.11, p=.001). Mindfulness training also showed significantly greater 1-week point prevalence abstinence post-treatment (36% vs. 15%, χ^2=3.5, p=.06) and at 17-weeks follow-up (31% vs. 6%, χ^2=6.3, p=.01). Notably, although both groups reported home practice as part of their assigned treatment, only the mindfulness training group showed significant correlations between home practice (i.e., meditation) and smoking outcomes, suggesting a specific effect of mindfulness training. We found that home practice significantly predicted a reduction in smoking (daily meditation: β =-1.21, p=.007; informal on-the-go practices: β =-1.52, p<.0001) and moderated the relationship between craving and smoking (β =.515, p=.026) [8]. In other words, the more an individual practiced mindfulness exercises, the less they smoked, and the amount of practice predicted a reduction in the association between craving and smoking. These findings suggest preliminary efficacy of mindfulness training for smoking cessation, and that the association between craving and smoking may be a plausible mechanistic target for treatment. Overall, recent reviews and our own work support mindfulness training as a candidate for smoking cessation treatment, and that "high-quality adequately powered RCTs should be conducted" [47].

A.4. Smartphone-based mindfulness interventions for smoking cessation

Despite these promising findings, in-person mindfulness training is challenged by the need for experienced therapists, significant time and cost demands, limited access to treatment and lack of

standardization, among other challenges [9]. One way to overcome these limitations is to deliver mindfulness treatments by smartphone apps. In addition to the general advantages of smartphone-based treatments for smoking discussed above, mindfulness interventions may be particularly suitable for the mobile platform as a means to access and bring careful attention to present moment experience [52] and because mindfulness is considered a state-like, context-dependent and dynamic mental behavior [42, 53]. Smartphone-based mindfulness interventions can be accessed any time a user encounters a cue, craving or affective state that increases the urge to smoke, can be triggered by smoking episodes, or can even be pushed to the smoker to bring awareness to triggers and cravings in advance of predicted smoking episodes as in this proposal. Getting mindfulness into the hand of the user may help bring awareness to the moment-to-moment body sensations, emotions and thoughts that constitute cue-reactivity, craving and affective states, to work with these experiences mindfully rather than react by smoking. We have recently completed a full-scale randomized controlled trial (*N*=505) of a smartphone app, Craving to Quit, that delivers mindfulness training for smoking cessation [4, 5]. We found that mindfulness training was feasible to deliver via smartphone app and although there were no significant differences in smoking abstinence rates at 6 months compared with a control app, we found that only mindfulness training lessened the association between craving and smoking across treatment. These findings suggest the utility and feasibility of delivering mindfulness interventions for smoking via smartphone app.

A.5. Craving is a plausible target for mindfulness interventions

As mentioned above, findings from both our randomized controlled trials of in-person and smartphone-based mindfulness training for smoking cessation indicated that mindfulness lessens the association between craving and smoking. Although the centrality of craving to smoking is disputed [54], craving is nevertheless a common concern among smokers who are trying to quit and one of the primary symptoms that smokers seek to alleviate through treatment [55]. However, few smoking cessation interventions target the association between craving and smoking. Quit smoking medications (buproprion, varenicline, nicotine patch) have been found to reduce background craving but not to prevent or alleviate craving induced by cues, thoughts or affective states [55]. Nicotine replacement therapies (nicotine gum, lozenge) have been found to provide relief from acute craving only once it has been triggered [55, 56], a substitution strategy (gum for cigarettes) that may not break the link between craving and smoking [7]. Only behavioral treatments that target reduced craving have been found to lessen the association between craving and substance use [57]. For example, targeted approaches of monitoring urges and “urge-surfing” were found to reduce the relationship between negative mood and alcohol craving, which predicted a reduction in drinking frequency in response to negative mood [58]. Similarly, Mindfulness-Based Relapse Prevention was found to reduce the relationship between negative affect and craving, which predicted a later reduction in substance use for drugs of abuse including alcohol, cocaine/crack, methamphetamine and polydrug use [59]. Finally, in a study of web-based acceptance and commitment therapy for smoking cessation, the difference in smoking quit rates versus control were mediated by increases in noticing and not acting on urges to smoke [60]. From a mechanistic perspective, mindfulness training targets craving by teaching smokers to become aware of cravings as they arise and investigate what they feel like in the body, emotions and thoughts, however uncomfortable or unpleasant, in order to learn to tolerate the physical sensations, emotions and thoughts and “ride out” cravings rather than react by smoking [7]. Instead of changing, suppressing, resisting or avoiding cravings, mindfulness helps individuals recognize, accept and investigate cravings and learn how to extinguish them rather than smoke [61]. In line with this, a recent review of mindfulness and craving studies suggested that mindfulness may lead to reductions in craving by extinction rather than suppression [62]. Mindfulness training has been found to reduce reactivity to craving cues [63] and stressors [64] among other changes [43] that may help lessen the association between craving and substance use. Cravings may continue to arise, as is evident by a comparable level of craving reported by experimental and control groups in our clinical trials, yet the positive relationship between craving and smoking may be reduced with mindfulness training. This suggests

that craving is a promising target for mindfulness interventions, particularly when mindfulness is delivered via smartphone to intervene with cravings in the moment.

A.6. Brief mindfulness interventions for smoking cessation

A major challenge for mindfulness interventions is the time required for training and practice. Time intensive treatments for smoking are generally underutilized, especially among minority, younger, and lower socioeconomic groups [65]. Most smokers make unaided quit attempts, thereby limiting the public health impact of smoking cessation treatment [65]. Similarly, attrition from treatment due to time burden has limited the clinical impact of mindfulness interventions [66]. Smartphones can greatly reduce this burden by enabling delivery of *brief* mindfulness interventions. Brief mindfulness practices may be more efficient, accessible and feasible to learn [53]. Brief mindfulness interventions for smoking (~2-10 minutes) have been associated with significant reductions in negative affect, cravings, withdrawal symptoms and smoking behavior [48, 67] and with significant increases in mindfulness [53], and have been correlated with outcomes as a component of larger mindfulness training programs for smoking cessation [8]. For example, a brief "urge-surfing" intervention – in which smokers attend to cravings and observe changes over time rather than smoke to alleviate craving – was found to reduce cigarettes per day at 1-week compared with control [67]. A brain imaging study reported that in-the-moment mindful attention reduced self-reported craving upon exposure to smoking cues and reduced functional connectivity between craving-related brain regions [63]. In another study, EMA data totaling nearly 2000 assessments indicated that a brief mindfulness exercise compared with control reduced negative affect, reduced craving immediately post-mindfulness practice and reduced cigarettes per day over time [68]. However, none of these studies provided brief mindfulness interventions at the moment of craving or smoking. The ability to deliver brief mindfulness exercises in context, to provide a short intervention at the critical moment of cues, cravings or affective states that trigger smoking, may significantly boost the efficacy of mindfulness interventions for smoking cessation. Therefore, this trial will test the feasibility of delivering brief mindfulness exercises by smartphone, triggered by smoking or pushed to the user in anticipation of cravings to smoke.

A.7. The approach in this trial

First, daily smokers will wear a smartband to monitor and detect smoking and will be notified of smoking episodes in real time. As discussed above, smoking can be habitual and "mindless" and self-monitoring of smoking behavior alone may reduce smoking [14]. Next, a "mindful smoking" exercise will be triggered by smoking episodes. Mindful smoking builds on the recognition of one's smoking behavior enabled by smartband-based monitoring and notification by bringing specific awareness to the present moment effects of smoking –the physical sensations, emotions and thoughts that result from smoking [52, 69]. Through mindful smoking, one gains a clear recognition of the present moment effects of smoking. A clear and nonjudgmental recognition of one's experience is considered to be a critical step for lasting habit change [69]. A thorough evaluation of the one's experience of smoking reveals that smoking is not necessarily as gratifying as once perceived, and this begins a process of disenchantment with smoking [52, 70]. Finally, a mindfulness exercise to help cope with cues, cravings and affective states will be delivered to the smoker prior to each predicted smoking episode according to their individualized smoking profile. This exercise teaches smokers how to work mindfully with triggers to smoke using RAIN [52]: Recognize, Allow, Investigate, Note/Not-identify. Smokers learn to (1) Recognize cues, cravings or affective states that trigger smoking; (2) Allow and accept their experience, however pleasant or unpleasant, without trying to change it; (3) Investigate what the experience feels like in the body, emotions and thoughts; and (4) Note/not-identify with what is happening from moment to moment. By openly investigating one's present moment experiences of craving in a nonjudgmental way, one learns that cravings are physical sensations, thoughts and emotions that will subside. RAIN practice was shown to directly moderate the dissociation of smoking from craving in our in-person trial of mindfulness training [3] and was associated with reduced craving to smoke in our trial of smartphone-based mindfulness training [4, 5]. Overall, this trial tests a three-step intervention in which smokers become aware of their smoking behavior and triggers by tracking

smoking; gain a clear recognition of the actual effects of smoking by mindful smoking; and learn to work mindfully with cravings and triggers rather than smoke using RAIN.

4. Research Plan: Summarize the study design and research procedures using non-technical language that can be readily understood by someone outside the discipline. Be sure to distinguish between standard of care vs. research procedures when applicable, and include any flowcharts of visits specifying their individual times and lengths. Describe the setting in which the research will take place.

D.1. Overview

This study will test the feasibility of a smartband/smartphone-based smoking detection and brief mindfulness intervention (Fig 1), described in detail below. An initial pilot study will be run using the same approach (N=10). First, smokers will wear a smartband for 21 days to automatically monitor and detect smoking and will be notified of smoking episodes in real time to bring attention to their smoking behavior. Their smoking data from this time will be used to develop individualized smoking profiles. They will be instructed to smoke as much or as little as they like [68] but will set a quit date at 30 days. This timing was chosen to balance motivation to quit with time to collect enough smoking tracking data to predict smoking behavior. All subjects will be encouraged at study onset to utilize quit smoking medications to help cope with nicotine withdrawal, to meet clinical guidelines [71] and as in our prior work [72] by directing them to the medications and nicotine replacement therapy pages of http://smokefree.gov. Next, they will be provided with information on how mindfulness could be useful to smokers and will be introduced to the brief mindfulness exercises as part of an online mindfulness training (15 min). The "mindful smoking" exercise will then be triggered by any detected smoking episode for 7 days prior to their quit date, to bring awareness to the present moment effects of smoking. Finally, for 30 days post-quit, the RAIN exercise will be delivered to smokers prior to each predicted smoking episode according to their individualized smoking profile, to help them cope with cravings. They will continue to wear the smartband to monitor for smoking, and any detected smoking episode (i.e., relapse) will trigger the mindful smoking exercise. More generally, smokers can "delay" or "skip" any mindfulness exercise and will be compensated for wearing the smartband as described below. Additionally, the mindfulness exercises will be accessible in their previous text messages for the smoker to use any time they have a craving to smoke. All interactions with the smartband app will be time stamped including onset/offset of mindfulness exercises. This trial will test the feasibility of the intervention including treatment fidelity, adherence and acceptability, to inform a larger randomized controlled efficacy trial.

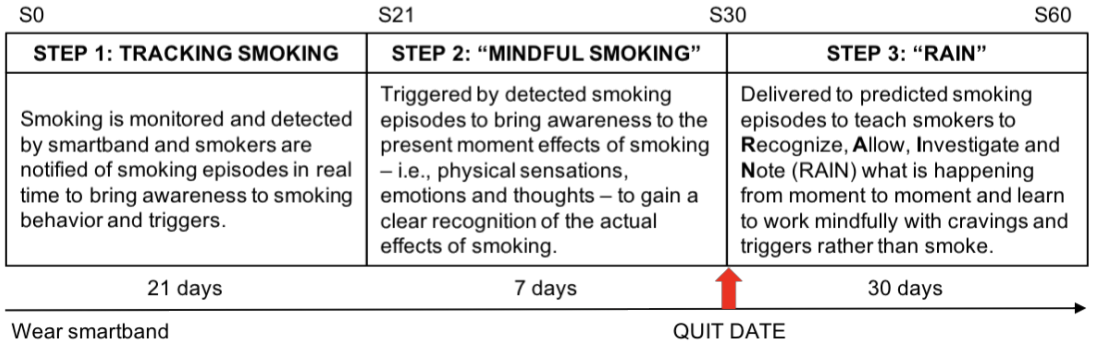

Figure 1. Smartband/smartphone-based mindfulness intervention overview. Daily smokers will wear a smartband for 21 days to automatically detect and notify them of smoking episodes and to obtain individualized smoking profiles. They will set a quit date at 30 days. For the 7 days prior to quitting, a "mindful smoking" exercise will be triggered by smoking. Finally, for 30 days post-quit, the "RAIN" exercise will be delivered to the smoker prior to each predicted smoking episode according to individualized smoking profile. Study surveys (S) will be conducted at baseline and days 21, 30 and 60 (end of study). Participants will wear the smartband throughout the study to detect and notify them of smoking episodes.

D.2. Participant flow

As previously [4, 5], online advertisements will link individuals to a dedicated study website offering smartband/smartphone-based treatment for smoking. Interested individuals will fill out a short online screening survey to determine eligibility and if eligible complete the online consent form to participate. Individuals will be excluded for making more than one attempt to complete the screening survey, as identified by matching contact information or IP address. They will then provide their contact and shipping information. They will be shipped a smartband and will be provided a "fake phone number" (i.e., download code) for the study app.

D.3. Onboarding

Upon receipt of their smartband, participants will take part in a zoom/online training during which they will be provided with step-by-step instructions on how to utilize the technology (i.e., onboarding). Onboarding involves instructing the user on how to pair the smartband with their smartphone, demonstrating how to wear and use the smartband and app, and reviewing the study procedures. Participants will receive $10 for onboarding. A researcher will be available throughout the study for support with any technical problems. Any technical support will be conducted using text, phone, email and/or Zoom and Skype for Business which have been approved for use with high risk data by Yale. After the onboarding session, participants will complete a baseline survey to assess demographics and other factors (see "Assessments").

D.4. Outcomes

Quit is defined based on proposed standards [73] as 7 day point prevalence abstinence and continuous abstinence (<5 cigs since quit date). E-cigarette use will not constitute a relapse but will be monitored and reported. Ratings (Likert items, e.g., timeliness) will be evaluated as % of participants and score range (very low, low, moderate, high, very high), with feasibility determined by 75% of participants rating an item as moderate or higher (Aim 1,3). Average responses for a given factor (e.g., satisfaction) on the User Experiences Questionnaire will be tested similarly, and qualitative analysis of open-ended questions will be used to further evaluate acceptability (Aim 3). Adherence cut-offs (e.g., time spent wearing the smartband) will be 80% (Aim 2). Adherence was high in pilot work (90% of participants answered 80% of smoking notifications[14]).

D.5. Assessments

Participants will be provided links to online surveys at baseline, 21 days, 30 days and 60 days (end of study) to measure smoking and other domains (Table 1) and to provide study instructions including initial mindfulness training (15 min). All surveys will be hosted on Yale Qualtrics secure survey software (https://yalesurvey.qualtrics.com) and optimized for delivery on mobile devices. The baseline survey will be automatically provided to eligible participants upon completing the screening survey and providing informed consent. All following surveys will be automatically emailed to the participant at each time point. For non-completed surveys a reminder text message will be sent at 1 and 2 days, followed by a phone call at 3 days. Demographics and smoking characteristics will be evaluated using standardized PhenX Toolkit protocols. Smoking status will include one-week point prevalence abstinence and continuous abstinence [73], cigarettes per day, and other tobacco use (e.g., e-cigarettes). All are standardized measures with documented psychometrics. In addition, across treatment, ratings are delivered as EMA after each mindfulness exercise and include helpfulness, timeliness, craving and affect. At the end of the study, active participants may be asked to take part in an optional debriefing to provide feedback about their experiences in the study.

Table 1. Assessments.

Instrument Name	Domain assessed	Baseline	Day 21	Day 30	Day 60
Demographics	Demographics	X			
Smoking status [73]	Smoking	X	X	X	X
Time Line Follow Back [74] (since last survey)	Daily smoking	X	X	X	X
Medication use questionnaire	Medications used	X	X	X	X
Fagerström Test for Nicotine Dependence [75]	Nicotine dependence	X	X	X	X
Minnesota Nicotine Withdrawal Scale [76]	Withdrawal symptoms	X	X	X	X
Five Facet Mindfulness Questionnaire [77]	Mindful awareness	X	X	X	X
User experience questionnaire*	User feedback, acceptability		X	X	X
Optional debriefing phone call	User feedback, acceptability				X

*The User Experiences Questionnaire [15] includes rating mindfulness exercises (useful, timely, dose, overall timeline); satisfaction (likability, enjoyment, visual appeal, speed, functionality); burden (perceived effort required to participate); intent to continue to use (use or tell friends to use outside of the study); and technology (video, sound, image content, functionality, misuse, suggested improvements).

D.7. Smoking monitoring, detection and notification

SmokeBeat (now called SafeBeing) uses a proprietary machine-learning algorithm to identify the hand-to-mouth gestures that characterize smoking a cigarette and differentiate these from other similar hand gestures for a given individual. Briefly, raw data are collected from the accelerometer and gyroscope sensors, and following data stabilization and noise filtering, the algorithm determines which movements being performed by the individual signify smoking. Upon smoking detection (3 puffs) the user is asked to confirm or deny smoking (Fig 2). If confirmed, the algorithm learns about the individualized parameters for that smoker. If it turns out to be a false positive, the algorithm learns that as well. In case of misses, the user can report any undetected smoking episode ("Have you smoked, and we didn't notice?"). This allows the algorithm to learn smoking gestures for the individual smoker and integrate those into a user configuration file, which is continually updated. In this trial, participants will wear a smartband on the hand used for smoking during waking hours for 60 days total. They will receive a notification on their smartband and smartphone when smoking is detected and will be asked to confirm or deny smoking. The notification will remain until the user responds. As stated, they can additionally report any missed smoking episodes. Finally, users can actively search the app for statistical information regarding their smoking patterns, but this information will never be pushed to the user.

D.8. Brief mindfulness interventions

a. Mindfulness instructions

Study instructions will be provided via the survey for each study time point (Fig 1). After an initial 21 days of smoking monitoring, detection and notification [14], users will receive by email a link to a brief (max 15 min) online mindfulness training, including information on how mindfulness could be useful to smokers and an introduction to the mindfulness exercises (as previously [4, 5]). They will be reminded of their quit date in one week and will be instructed to "smoke mindfully" for the next week by completing the mindful smoking exercise that will be triggered by detected smoking episodes and self-reported smoking or can be accessed any time from the app home page. They will be reminded that after one week (i.e., after their quit date), they will be pushed the RAIN exercise at each time each day that they typically smoke a cigarette, to help them cope with cravings, for 30 days. They will be reminded that the mindful smoking exercise will continue to be triggered any time they smoke.

Additional instructions will be provided about how to delay or skip an exercise. Finally, they will be reminded of the upcoming surveys and of the compensation for completing the surveys, wearing the smartband, and of the study bonus.

b. Mindful smoking exercise

For the next 7 days, upon detection and confirmation or self-report of smoking, a mindful smoking exercise will be automatically delivered to the user via the smartphone app. They will first be asked to confirm or deny smoking. Next, the mindful smoking exercise will be delivered as a 2-minute audio-guided mindfulness practice with subtitles. After completing the mindful smoking exercise, they will be asked “How helpful did you find this exercise?” (visual analog scale [VAS] “very helpful” to “not at all”).

c. RAIN exercise

For the subsequent 30 days, the RAIN exercise will be automatically delivered to the user via the smartphone app prior to each predicted smoking episode according to individual smoking profiles obtained as described below. They will first be asked to rate their craving (“How much are you craving a cigarette?” VAS “very much” to “not at all”) and affect (“How are you feeling?” VAS “very bad” to “very good” [105]). Next, they will be prompted to complete the RAIN exercise, also delivered as a 2-minute audio-guided mindfulness practice with subtitles. After completing RAIN, they will be asked “How helpful did you find this exercise?” (VAS “very helpful” to “not at all”); “How was the timing of this exercise?” (VAS “too early” to “too late”); and to again rate their craving and affect.

D.9. Individualized smoking profiles

Individualized smoking profiles will be obtained using smartband data tracking smoking across the first 21 days of the study, based on the maximum information possible: (1) average times each cigarette is smoked each day; (2) average times each cigarette is smoked on weekdays versus weekends; (3) average time between cigarettes; (4) average wake/sleep time; and (5) average cigarettes per day each day. Less predictable smokers will have less data to inform the prediction algorithm. At the very least, their waking hours will be divided by the number of cigarettes smoked per day and a prompt will be sent at random times in each interval. How much smartband tracking data is needed to adequately develop an individualized smoking profile is a main question in this feasibility trial. We will use this data to then deliver RAIN to the user for 30 days after their quit date. RAIN will be delivered 5 minutes prior to each predicted smoking episode during waking hours.

D.10. Adherence

Adherence to wearing the smartband will be monitored daily and participants will be sent automated reminders and/or text message reminders if their smartband is not active for 12-24 hours, followed by a phone call if their smartband is not active for 2 days. As an incentive, participants will be paid $1/day to wear the smartband during waking hours (≥12 hours/day; current smartband battery life is 3 days). Mindfulness and RAIN exercise completions will also be monitored daily, and participants will be sent either a rewarding text message if there is at least one completion from the day before, or an encouraging text message if the participant did not complete any exercises the day before. Additionally, to encourage participation in mindfulness training, we will add $10 for completing the initial mindfulness instructions. Finally, there will be a study completion bonus of $50.

To improve adherence, study compensation will be: $10 upon completion of the zoom/online training, $20 upon completion of the second study survey, and $10 upon completion of the third study survey. At the end of the study, they will be paid $1 per day for each day of the 60-day study that they have worn their smartband for 12 waking hours (up to $60). At the end of the study, they will also be paid $10 for the end of study survey, and a $50 bonus payment if they have completed all parts of the study. **Total study payment will be up to $160** (up to $40 paid upon each survey completion, up to $120 paid at

the end of the study). Please note that all study equipment (smartband, CO-monitor, if applicable) must be returned before the final study payment. Finally, they may be invited to take part in an optional debriefing at the end of the study, for which they will be paid an additional $10.

5. Genetic Testing N/A ☒

6. **Subject Population:** Provide a detailed description of the types of human subjects who will be recruited into this study.

   Participants (N=110: n=10 for the pilot study, n=100 for the feasibility trial): Inclusion criteria: (a) at least 18 years of age; (b) daily smokers (≥5 CPD); (c) for at least 2 years; (d) own an Android phone or iPhone; (f) fluent in English as content is only available in English*; and (g) motivated to quit smoking, as indicated by ≥ 18 of 20 on the Action subscale of the Readiness to Change Questionnaire [78] as previously [4, 5]. Exclusion criteria: (a) e-cigarette use (some days/every day) because the smartband technology is not yet able to distinguish e-cigarette use. Recent reports indicate that 10.6% of current cigarette smokers had used e-cigarettes in the past 30 days and 3.6% regularly use e-cigarettes (≥20 of the past 30-days) [79]. Therefore, we do not expect dual use to negatively impact recruitment. Other tobacco product use including e-cigarettes will be monitored at each time point (see "Assessments"). No other exclusion criteria. Possible confounds include concurrent use of quit smoking and other psychotropic medications. These will be monitored for confounding effects using our medication use questionnaire.

   *Materials will be developed in Spanish during the course of this research, however only English-speaking individuals will be currently enrolled.

7. **Subject classification:** Check off all classifications of subjects that will be specifically recruited for enrollment in the research project. Will subjects who may require additional safeguards or other considerations be enrolled in the study? If so, identify the population of subjects requiring special safeguards and provide a justification for their involvement.

☐Children	☐ Healthy	☐Fetal material, placenta, or dead fetus
☐Non-English Speaking	☐ Prisoners	☐Economically disadvantaged persons
☐Decisionally Impaired	☐ Employees	☐Pregnant women and/or fetuses
☐Yale Students	☐ Females of childbearing potential	

NOTE: Is this research proposal designed to enroll children who are wards of the state as potential subjects?

Yes ☐ No ☒

8. **Inclusion/Exclusion Criteria:** What are the criteria used to determine subject inclusion or exclusion?

   Inclusion criteria: (a) At least 18 years of age; (b) daily smokers (≥5 CPD); (c) for at least 2 years; (d) own an Android phone or iPhone; (f) fluent in English as content is only available in English; and (g) motivated to quit smoking, as indicated by ≥ 18 of 20 on the Action subscale of the Readiness to Change Questionnaire 90 as previously [4, 5].

   Exclusion criteria: (a) e-cigarette use (some days/every day) because the smartband technology is not yet able to distinguish e-cigarette use. Recent reports indicate that 10.6% of current cigarette smokers had used e-cigarettes in the past 30 days and 3.6% regularly use e-cigarettes (≥20 of the

past 30-days) [79]. Therefore, we do not expect dual use to negatively impact recruitment. Other tobacco product use including e-cigarettes will be monitored at each time point (see "Assessments").

No other exclusion criteria. Possible confounds include concurrent use of quit smoking and other psychotropic medications. These will be monitored for confounding effects using our medication use questionnaire at each study time point.

9. How will **eligibility** be determined, and by whom? Write here

As previously [4, 5], online advertisements will link individuals to a dedicated study website offering smartband/smartphone-based treatment for smoking. Interested individuals will fill out a short online screening survey to determine eligibility and if eligible complete the online consent form to participate. Individuals will be excluded for making more than one attempt to complete the screening survey as indicated by duplicate contact information or IP address.

10. **Risks:** Describe the reasonably foreseeable risks, including risks to subject privacy, discomforts, or inconveniences associated with subjects participating in the research.

This study involves wearing a smartband to monitor, record and reduce smoking; with additional notifications, mindfulness exercises and app-based questions (i.e., confirm/deny smoking, rate quit smoking messages) and surveys at each time-point. All study procedures are mobile/online. The alternative to participation is not to participate. The potential risks are minor.

1. Research measurements – Smoking monitoring, smoking self-report, app-based notifications and ecological momentary assessments (i.e., ratings), and study surveys. All are noninvasive and should add no risk. The major disadvantage is the time taken to complete them and that they may disrupt other activities.
2. Loss of confidentiality – Data at risk for loss of confidentiality include online survey data and app-based data.
3. Nicotine withdrawal – Subjects may experience nicotine withdrawal such as craving cigarettes, mild anxiety, restlessness, irritability, difficulty concentrating, loss of energy and excessive hunger. These are normal symptoms that people get when they do not smoke, and they can be uncomfortable but are not life threatening. They are minimal compared to the health risks of continued smoking.

11. **Minimizing Risks:** Describe the manner in which the above-mentioned risks will be minimized.

(i) Research measurements: Our past experience with these and related measures indicates that they are acceptable to subjects.

(ii) Confidentiality:

i. Limits to confidentiality: Participants will be informed that the research material collected will be for research purposes only. All participants will be specifically told that we will not reveal any personal information collected as part of the research procedures, including their reported substance use. However, there is always the possibility that participation in this study may make others, such as friends and family members, aware of their information. They will be told that if they do not feel comfortable with this, then they should not participate. However, they will be told that if they report any information to us about abuse or homicidal or suicidal behavior, we will be required to report this information to the appropriate authorities. They will be informed that their de-identified data will be shared with NIH. All limits to confidentiality will be explained to all participants. Specifically, they will be told that we will protect the participant's confidentiality and that we will not share any personal information. This will be clearly stipulated in the consent forms.

ii. Data collection and storage: Data collection and storage will be conducted according to standardized protocols. All research data collection and storage will be managed by Yale personnel who have received the proper training by Yale to ensure that research is in compliance with the current applicable laws, regulations and Yale's policies and procedures in support of the protection of research participants. All research personnel are required to participate in and document training in protection of human subjects and the responsible conduct of scientific research. Only authorized research personnel will have access to the information gathered in this study. All study data will ultimately reside on Yale encrypted computers. Quantitative data will be entered into a password-protected SPSS database. The organizational structure used to ensure quality of data in this study include: (a) preliminary review of all data for completeness and coding errors by the PI; and (b) utilization of error- checking statistical procedures. All information will be identified by code and will not be linked to personally-identifying information. Patient names or other identifiers such as social security number, initials, birth date will not be used to identify any records. Only a code number will identify the individual research records. The code number will not be based on any information that could be used to identify the subjects (for example, social security number, initials, birth date, etc.). The master list linking names to code numbers will be kept separately from the research data on Yale encrypted computers. Only approved members of the research team will have access to personally-identifying information (e.g., phone numbers, addresses). This information will be stored separately on Yale encrypted computers.

iii. App data: App data is collected, managed and stored according to standardized protocols at Somatix, Inc. Data is collected from the smartphone app to the Somatix backend platform and to the database running over Hypertext Transfer Protocol for secure communication (HTTPS). All data is stored on Amazon Web Services (AWS) - Cloud Computing, Relational Database Service (Amazon RDS) for MySQL, secured using Amazon's advanced capabilities. Any personal-identifying information (e.g., location) will be encrypted in the database. Only authorized Somatix, Inc. personnel will have access to this database. The database will only be accessed by Somatix's password-protected computers. The participant will be identified only by a fake phone number in Somatix database. Somatix will not have access to the key linking a participant's personal information (real phone number) to this fake phone number. Only the fake phone number will be associated with the participant's data in the Somatix database.

(iii) Nicotine withdrawal: Nicotine withdrawal can be uncomfortable but is not life threatening and the risks are minimal compared to the health risks of continued smoking. Subjects will be provided information on how to best tolerate their withdrawal symptoms. Subjects will be encouraged at study initiation to use nicotine replacement therapy and quit smoking medications, by referring them to medications information on https://smokefree.gov.

(iv) The involvement of Somatix Inc. does not engage them in human subjects research, therefore human protection training is not required by Yale. To ensure that the company securely maintain the study data, we have obtained the required Security Design Review (SDR) by Yale's Information Security Department and establish a Business Associate Agreement between Yale's HIPAA Privacy Office and Somatix Inc. The SDR process ensures that the security and application of systems are in line with best practices and standards at Yale.

12. Data and Safety Monitoring Plan: Include an appropriate Data and Safety Monitoring Plan (DSMP) based on the investigator's risk assessment stated below. (Note: the HIC will make the final determination of the risk to subjects.)

a. What is the investigator's assessment of the overall risk level for subjects participating in this study?

Minimal risk

b. If children are involved, what is the investigator's assessment of the overall risk level for the children participating in this study?

NA

c. Include an appropriate Data and Safety Monitoring Plan. Examples of DSMPs are available here http://your.yale.edu/policies-procedures/forms/420-fr-01-data-and-safety-monitoring-plans-templates for

i. Minimal risk
ii. Greater than minimal

A formal Data and Safety Monitoring Plan has been made for this study in line with NCCIH guidelines (see attached).

Briefly, the Principal Investigator (Dr. Garrison) will be responsible for assuring protocol compliance and conducting quarterly safety reviews which will be provided for review to the Independent Study Monitoring Committee. During the review process, the Principal Investigator will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment.

This monitoring will be consistent with NIH policy regarding the protection of human subjects in research, and FDA guidance on statistical practices for clinical trials (ICH E9) and good clinical practices (ICH E6). In general, the data to be reviewed will include screening data, baseline data, efficacy data, and safety data.

This project presents minimal risks to the subjects and adverse events or other problems are not anticipated. The Principal Investigator will conduct a review of all adverse events and determine the attribution and grade of severity of the adverse event by using the following scales:

Attribution of Risk Categories:
Definite: Adverse event(s) will clearly be related to investigational agent(s) or other intervention
Probable: Adverse event(s) will likely be related to investigational agent(s)
Possible: Adverse event(s) may be related to investigational agent(s)
Unlikely: Adverse event(s) will doubtfully be related to investigational agent(s)
Unrelated: Adverse event(s) will clearly not be related to the investigational agents(s)

Grades of Risk:
0: No adverse event or within normal limits
1: Mild adverse event
2: Moderate adverse event
3: Severe adverse event resulting in hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect
4: Life-threatening or disabling adverse event
5: Fatal adverse event

This process is described in more detail in the Data and Safety Monitoring Plan (attached).

In the unlikely event that such events occur, serious and unanticipated and related adverse events or unanticipated problems involving risks to subjects or others will be reported immediately (if possible), followed by a written report within 7 calendar days of the Principal Investigator becoming aware of the

event to the Yale IRB, Independent Monitoring Monitor(s), and NCCIH. Any other unanticipated problem will be reported to the IRB, Independent Safety Monitor(s), and NCCIH within 14 days of the PI becoming aware of the problem.

To ensure that the design, conduct, and reporting of research for this project is free from bias resulting from Investigator financial conflicts of interest, the project will be conducted in accordance with NIH Financial Conflict of Interest (FCOI) regulation, *Responsibility of Applicants for Promoting Objectivity in Research for which PHS Funding is Sought* (42 CFR Part 50 Subpart F), applicable to grants and cooperative agreements (2011 Revised Regulations) and Yale University Policy on Conflict of Interest.

13. Statistical Considerations: Describe the statistical analyses that support the study design.

Overview: Quit is defined based on proposed standards [73] as 7 day point prevalence abstinence and continuous abstinence (<5 cigs since quit date). E-cigarette use will not constitute a relapse but will be monitored and reported. Ratings (Likert items, e.g., timeliness) will be evaluated as % of participants and score range (very low, low, moderate, high, very high), with feasibility determined by 75% of participants rating an item as moderate or higher. Average responses for a given factor (e.g., satisfaction) on the User Experiences Questionnaire will be tested similarly, and qualitative analysis of open-ended questions will be used to further evaluate acceptability. Adherence cut-offs (e.g., time spent wearing the smartband) will be 80%. Adherence was high in pilot work (90% of participants answered 80% of smoking notifications [14]).

Aim 1. To assess treatment fidelity for a smartband/smartphone-based mindfulness intervention: *(1) Whether we can accurately detect smoking episodes* will be determined by the percent of smoking episodes detected and the rate of false alarms in the first 21 days of the study during which smokers are wearing the smartband to track smoking and upon smoking detection are asked to confirm or deny smoking and self-report any undetected smoking episodes. We expect to replicate previous findings of >80% detection and negligible rate of false alarms [14]. *(2) Whether we can deliver mindful smoking triggered by smoking episodes* will be determined by the percent of mindful smoking exercises correctly triggered by detected smoking episodes and the rate of false alarms in the next 7 days of the study during which any detected smoking episode triggers a prompt that first asks the smoker to confirm or deny smoking and then launches the mindful smoking exercise. Again, we expect to replicate previous findings of >80% detection and negligible rate of false alarms [14]. *(3) Whether we can deliver RAIN to predicted smoking episodes* will be measured as average timeliness ratings in the next 30 days of the study during which RAIN is delivered prior to predicted smoking episodes and the smoker is asked to rate whether the exercise was delivered on time. Additionally, we will analyze the craving ratings obtained before participants complete RAIN, as a proxy for whether or not we have targeted moments of high craving. Ratings (Likert items for timeliness, craving) will be evaluated as % of participants and score range (very low, low, moderate, high, very high), with feasibility determined by 75% of participants rating an item (timeliness, craving) as moderate or higher. We expect on average moderate to high timeliness and craving ratings, suggesting that RAIN was delivered in time to help cope with cravings. These and other aspects of treatment fidelity will be reported according to recommended guidelines [17].

Aim 2. To assess adherence to a smartband/smartphone-based brief mindfulness intervention: Adherence will be measured as: (1) percent of time spent wearing the smartband across the study; (2) percent of smoking notifications answered (i.e., confirmed or denied) across the study; (3) percent of mindful smoking exercises completed; (4) percent of EMA ratings answered; and (5) percent of RAIN exercises completed. We expect a high response rate based on an earlier study in daily smokers (12±2.9 CPD) in which 93% of smartband-based smoking notifications were responded to and 90% of

the participants answered more than 80% of the notifications [14]. Additionally, in our trial of smartphone-based mindfulness training, response rates to EMA were high at 3±2 assessments per day evaluating craving, smoking and other factors [4, 5]. Adherence cut-offs (e.g., time spent wearing the smartband) will be 80%. Adherence was high in pilot work (90% of participants answered 80% of smoking notifications [14]).

Aim 3. To assess acceptability of a smartband/smartphone-based brief mindfulness intervention: Immediately following each brief mindfulness exercise, smokers will be asked "How helpful did you find this exercise?" Acceptability will be measured as mean helpfulness ratings, separately for mindful smoking and RAIN. Helpfulness will be evaluated as % of participants and score range (very low, low, moderate, high, very high), with feasibility determined by 75% of participants rating helpfulness as moderate or higher. Acceptability will additionally be evaluated from feedback on the User Experiences Questionnaire[15] which includes rating mindfulness exercises (useful, timely, dose, overall timeline); satisfaction (likability, enjoyment, visual appeal, speed, functionality); burden (perceived effort required to participate); intent to continue to use (use or tell friends to use outside of the study); and technology (video, sound, image content, functionality, misuse, suggested improvements). Average responses for a given factor (e.g., satisfaction) on the User Experiences Questionnaire will be evaluated similarly to ratings, and qualitative analysis of open-ended questions will be used to further evaluate acceptability. For example, we will evaluate the acceptability of the number of notifications/interventions, which are essentially matched to true/predicted cigarettes per day.

Secondary data analysis: As a secondary aim, we will evaluate change in smoking (cigarettes per day) and abstinence at the end-of-study survey. Abstinence will be measured by: 1) self-reported one week point prevalence abstinence and continuous abstinence (> 5 cigarettes since quit date), 2) automatic smartband smoking monitoring and detection for 7 days prior to the assessment, and, 3) a random subset of individuals (50%) who report one-week point-prevalence abstinence at end-of-study will be shipped carbon monoxide breath monitors (coVita, LLC), or saliva kits (Alere iScreen OFD Cotinine Saliva Test) to confirm abstinence from smoking (<10 ppm or negative saliva test) via video chat with a researcher as previously [4, 5] or by submitting a recorded video via email or text. Abstinence rates will be reported for each measure. These data will be used to provide preliminary evidence about whether smartband-based smoking monitoring can inform measures of abstinence. We will use descriptive statistics to inform future studies. Additionally, all interactions with the app will be automatically tracked and evaluated related to engagement and secondary outcomes.

Missing data: In our recent trial [4, 5], most individuals dropped out upon enrollment. Treatment starters used the app 17±8 out of 22 days and completed ratings (EMA) on14±9 days. We then had 53% treatment completers –defined as 60% of treatment. Retention to the primary 6mo. survey was 84% despite whether subjects had engaged with treatment. Therefore, we do not anticipate significant missing survey data. We are unable to estimate retention at each step but will measure this. Relevant to our aims, other missing data may include smoking data from not wearing the smartband, or ratings data. Primary analyses will use missing at random (MAR) assumptions but we will also perform sensitivity analyses under reasonable missing not at random (MNAR) [80, 81]. For singly-measured outcomes we will use multiple imputation [82, 83] under MAR (primary) and MNAR (secondary analyses). For longitudinal outcomes, our primary approach will be full-information maximum likelihood under MAR [84]. We will fit pattern mixture longitudinal models to test the effect of deviations from MAR [85]. We will compare retained vs. dropouts on different characteristics to inform the MNAR models.

SECTION II: RESEARCH INVOLVING DRUGS, BIOLOGICS, RADIOTRACERS, PLACEBOS AND DEVICES

If this section (or one of its parts, A or B) is not applicable, check off N/A and delete the rest of the section.

A. RADIOTRACERS ☒N/A

B. DRUGS/BIOLOGICS ☒N/A

C. DEVICES ☒N/A

SECTION III: RECRUITMENT/CONSENT AND ASSENT PROCEDURES

1. Targeted Enrollment: Give the number of subjects:
   a. Targeted for enrollment at Yale for this protocol: N=110 but we will enroll N=150 to account for estimated high attrition as in our previous randomized clinical trial of a smartphone app for smoking cessation and other similar trials.
   b. If this is a multi-site study, give the total number of subjects targeted across all sites: *Write here*

2. Indicate recruitment methods below. Attach copies of any recruitment materials that will be used.

☒ Flyers	☒ Internet/web postings	☐ Radio
☐ Posters	☐ Mass email solicitation	☐ Telephone
☐ Letter	☒ Departmental/Center website	☐ Television
☐ Medical record review*	☐ Departmental/Center research boards	☐ Newspaper
☐ Departmental/Center newsletters	☒ Web-based clinical trial registries	☒ Clinicaltrails.gov
☒ YCCI Recruitment database	☒ Social Media (Twitter/Facebook):	
☒ Other:		

Google, Facebook, Reddit ads

* Requests for medical records should be made through JDAT as described at
http://medicine.yale.edu/ycci/oncore/availableservices/datarequests/datarequests.aspx

3. Recruitment Procedures:
   a. Describe how potential subjects will be identified. *Write here*
   b. Describe how potential subjects are contacted. *Write here*
   c. Who is recruiting potential subjects? *Write here*

As previously [4, 5], online advertisements will link individuals to a dedicated study website offering smartband/smartphone-based treatment for smoking. Interested individuals will fill out a short online screening survey to determine eligibility. Our advertising consultant (Kevin Danaher) will run the online advertising recruitment effort that does not involve any personally identifying information. Potential participants only put PHI into the screening survey accessed only by HIC approved members of the research team. To meet our targeted enrollment, we will use demographic and geographic targeted advertising, including targeted ads to men, older individuals, individuals with lower income and education, and specific geographic regions. We will use guidelines from the NIH toolkit, "Primary

Barriers and Facilitators to Participation in Clinical Research": 1) compensation, 2) short/flexible appointments, 3) clear communication in all study materials, 4) good relationships to improve retention, 5) constant contact through follow-up; and from recent work on barriers to participation in mHealth research [86]: 6) clear explanation of the technology, 7) increased sensitivity to data privacy and confidentiality, 8) systematic tracking of critical factors such as language preference, country of origin, health literacy and socioeconomic status at screening and enrollment to identify points at which underserved communities are selected out, to inform the larger trial. If we are not meeting our targeted recruitment, additional efforts will be made such as flyers, websites and recruitment databases, as indicated above.

4. Assessment of Current Health Provider Relationship for HIPAA Consideration:

Does the Investigator or any member of the research team have a direct existing clinical relationship with any potential subject?

☐Yes, all subjects

☐Yes, some of the subjects

☒No

If yes, describe the nature of this relationship. *Write here*

5. Request for waiver of HIPAA authorization: (When requesting a waiver of HIPAA Authorization for either the entire study, or for recruitment purposes only. Note: if you are collecting PHI as part of a phone or email screen, you must request a HIPAA waiver for recruitment purposes.)

Choose one:

☒ For entire study

☐ For recruitment/screening purposes only

☐ For inclusion of non-English speaking subject if short form is being used and there is no translated HIPAA research authorization form available on the University's HIPAA website at hipaa.yale.edu.

i. Describe why it would be impracticable to obtain the subject's authorization for use/disclosure of this data: *Write here*

ii. If requesting a waiver of signed authorization, describe why it would be impracticable to obtain the subject's signed authorization for use/disclosure of this data:

We are requesting a waiver of signed authorization for the entire study. Subjects from across the United States will enroll online, receive treatment via their smartphones, and perform all assessments online. It is impossible-and contrary to the structure of the study-to meet any of the subjects face-to-face.

The investigator assures that the protected health information for which a Waiver of Authorization has been requested will not be reused or disclosed to any person or entity other than those listed in this application, except as required by law, for authorized oversight of this research study, or as specifically approved for use in another study by an IRB.

Researchers are reminded that unauthorized disclosures of PHI to individuals outside of the Yale HIPAA-Covered entity must be accounted for in the "accounting for disclosures log", by subject name, purpose, date, recipients, and a description of information provided. Logs are to be forwarded to the Deputy HIPAA Privacy Officer.

6. Process of Consent/Assent: Describe the setting and conditions under which consent/assent will be obtained, including parental permission or surrogate permission and the steps taken to ensure subjects' independent decision-making.

   As previously [4, 5], online advertisements will link individuals to a dedicated study website offering smartband/smartphone-based treatment for smoking. Interested individuals will fill out a short online screening survey to determine eligibility and if eligible complete the online consent form to participate. Individuals will be excluded for making more than one attempt to complete the screening survey. The informed consent form will be provided online to subjects in advance of participation. The consent form includes a description of the project, describes the study procedures, risks and inconveniences, benefits, treatment alternatives, confidentiality, voluntary participation and withdrawal, economic considerations, and investigator contact information. A subject will encounter the online consent form when they are deemed eligible for the study after completing a short screening survey. Because there will be no one to explain the consent form, it will be as short, concise, and clear as possible for ease of understanding. If a potential subject has any questions regarding the study or consent form, they will be able to email or call one of the study investigators. Although subjects will not be able to be assessed to ensure their understanding of consent procedures, there is minimum to no risk in participating in the study and a subject can quit at any time by stopping their participation. Subjects who wish to participate will click "I accept". A copy of the consent form will be automatically emailed to the subject. We have used this approach previously in online/mobile technology-based research studies.

7. Evaluation of Subject(s) Capacity to Provide Informed Consent/Assent: Indicate how the personnel obtaining consent will assess the potential subject's ability and capacity to consent to the research being proposed.

   A few questions will be included after the online consent form to evaluate whether the subject understands the study procedures. They will only be enrolled (i.e., shipped the study smartband) if they indicate understanding the study procedures. They will be provided with study contact information (text, email) if they do not understand study procedures. Although subjects will not be able to be assessed in-person to ensure their understanding of consent procedures there is minimum to no risk in participating in the study and a subject can quit at any time by stopping their participation.

8. Non-English Speaking Subjects: Explain provisions in place to ensure comprehension for research involving non-English speaking subjects. If enrollment of these subjects is anticipated, translated copies of all consent materials must be submitted for approval prior to use.

   This study will not include non-English speaking subjects

As a limited alternative to the above requirement, will you use the short form* for consenting process if you unexpectedly encounter a non-English speaking individual interested in study participation and the translation of the long form is not possible prior to intended enrollment? YES ☐ NO ☒

Note* If more than 2 study participants are enrolled using a short form translated into the same language, then the full consent form should be translated into that language for use the next time a subject speaking that language is to be enrolled.

Several translated short form templates are available on the HRPP website (yale.edu/hrpp) and translated HIPAA Research Authorization Forms are available on the HIPAA website (hipaa.yale.edu). If the translation of the short form is not available on our website, then the translated short form needs to be submitted to the IRB office for

approval via modification prior to enrolling the subject. ***Please review the guidance and presentation on use of the short form available on the HRPP website.***

If using a short form without a translated HIPAA Research Authorization Form, please request a HIPAA waiver in the section above.

9. Consent Waiver: In certain circumstances, the HIC may grant a waiver of signed consent, or a full waiver of consent, depending on the study. If you will request either a waiver of consent, or a waiver of signed consent for this study, complete the appropriate section below.

☐Not Requesting any consent waivers

☒Requesting a waiver of signed consent:

☐ Recruitment/Screening only *(if for recruitment, the questions in the box below will apply to recruitment activities only)*

☒ Entire Study (Note that an information sheet may be required.)

For a waiver of signed consent, address the following:

- Would the signed consent form be the only record linking the subject and the research? YES ☐ NO ☐
- Does a breach of confidentiality constitute the principal risk to subjects? YES ☐ NO ☐

OR

- Does the research pose greater than minimal risk? YES ☐ NO☒
- Does the research include any activities that would require signed consent in a non-research context? YES ☐ NO ☒

☐ Requesting a waiver of consent:

☐ Recruitment/Screening only *(if for recruitment, the questions in the box below will apply to recruitment activities only)*

☐ Entire Study

For a full waiver of consent, please address all of the following:

- Does the research pose greater than minimal risk to subjects?
  - ☐ Yes *If you answered yes, stop. A waiver cannot be granted.*
  - ☐ No
- Will the waiver adversely affect subjects' rights and welfare? YES ☐ NO☐
- Why would the research be impracticable to conduct without the waiver? *Write here*
- Where appropriate, how will pertinent information be returned to, or shared with subjects at a later date? *Write here*

SECTION IV: PROTECTION OF RESEARCH SUBJECTS

Confidentiality & Security of Data:

1. What protected health information (medical information along with the HIPAA identifiers) about subjects will be collected and used for the research?

   The following data will be collected from all participants:

   1. Demographics, smoking characteristics and contact information (PHI include: name, address, email address, telephone number, Internet Protocol (IP) address, year of birth, age) – will be collected via the secure Yale Qualtrics Survey Tool (YaleSurvey.qualtrics.com), approved for use with EPI and EPHI records
   2. Survey data at each time-point – additional survey data (standardized questionnaires) will be collected via the secure Yale Qualtrics Survey Tool
   3. Smoking will be measured via smartband and smartphone app, managed by Somatix, Inc., and pushed to Yale using a coded subject identification number ("fake phone #").
   4. App notifications questions (i.e., confirm/deny smoking, ecological momentary assessments of craving, etc.) will be collected using a study app.
   5. App usage (e.g., onset/offset of mindfulness exercises) using Yale Secure Qualtrics.

2. How will the research data be collected, recorded and stored? *Write here*

   a. Data collection and storage: Data collection and storage will be conducted according to standardized protocols. All research data collection and storage will be managed by Yale personnel who have received the proper training by Yale to ensure that research is in compliance with the current applicable laws, regulations and Yale's policies and procedures in support of the protection of research participants. All research personnel are required to participate in and document training in protection of human subjects and the responsible conduct of scientific research. Only authorized research personnel will have access to the information gathered in this study. All study data will ultimately reside on Yale encrypted computers. Quantitative data will be entered into a password-protected SPSS database housed on Yale encrypted computers. The organizational structure used to ensure quality of data in this study include: (a) preliminary review of all data for completeness and coding errors by the PI; and (b) utilization of error-checking statistical procedures. All information will be identified by code and will not be linked to personally-identifying information. Patient names or other identifiers such as social security number, initials, birth date will not be used to identify any records. Only a code number will identify the individual research records. The code number will not be based on any information that could be used to identify the subjects (for example, social security number, initials, birth date, etc.). The master list linking names to code numbers will be kept separately from the research data on Yale encrypted computers. Only approved members of the research team will have access to personally-identifying information (e.g., phone numbers, addresses). This information will be stored separately on Yale encrypted computers.

   b. App data: App data is collected, managed and stored according to standardized protocols at Somatix, Inc. Data is collected from the smartphone app to the Somatix backend platform and to the database running over Hypertext Transfer Protocol for secure communication (HTTPS). All data is stored on Amazon Web Services (AWS) - Cloud Computing, Relational Database Service (Amazon RDS) for MySQL, secured using Amazon's advanced capabilities. Any personal-identifying information (e.g., location) will be encrypted in the database. Only authorized Somatix, Inc. personnel will have access to this database. The database will only be accessed by Somatix's password-protected computers. The participant will be identified only by a fake phone number in Somatix database. Somatix will not have access to the key linking a participant's personal information (real phone number) to this fake phone number. Only

the fake phone number will be associated with the participant's data in the Somatix database.

3. How will the digital data be stored? ☐CD ☐DVD ☐Flash Drive ☐Portable Hard Drive ☒Secured Server ☒Laptop Computer ☒Desktop Computer ☒Other AWS
4. What methods and procedures will be used to safeguard the confidentiality and security of the identifiable study data and the storage media indicated above during and after the subject's participation in the study?

Data collection and storage will be conducted according to standardized protocols. All research personnel are required to participate in and document training in protection of human subjects and the responsible conduct of scientific research. All information will be identified by code and will not be linked to subject name except as described above. All data analyses will be performed under approved HIC protocols. Hardcopies of the questionnaires without identifying information will be stored in a locked file cabinet in the study office All storage media will be password protected using Yale approved protocols.

To ensure that the Somatix, Inc., securely maintain the study data, we have obtained the required Security Design Review (SDR) by Yale's Information Security Department and establish a Business Associate Agreement between Yale's HIPAA Privacy Office and Somatix, Inc. The SDR process ensures that the security and application of systems are in line with best practices and standards at Yale.

All portable devices must contain encryption software, per University Policy 5100. If there is a technical reason a device cannot be encrypted please submit an exception request to the Information Security, Policy and Compliance Office by clicking on url http://its.yale.edu/egrc or email it.compliance@yale.edu

5. What will be done with the data when the research is completed? Are there plans to destroy the identifiable data? If yes, describe how, by whom and when identifiers will be destroyed. If no, describe how the data and/or identifiers will be secured. *Write here*

Data collected in the study will reside in our electronic storage mechanism for 7 years. All data analyses (deidentified and coded as described above) will be performed under approved HIC protocols.

6. If appropriate, has a Certificate of Confidentiality been obtained?

This project has NIH funding (1R34AT010365-01) and therefore a CoC was automatically issued in accordance with NIH CoC Policy (NOT-OD-17-109).

SECTION V: POTENTIAL BENEFITS

Potential Benefits: Identify any benefits that may be reasonably expected to result from the research, either to the subject(s) or to society at large. (Payment of subjects is not considered a benefit in this context of the risk benefit assessment.)

By participating in this research participants will receive free smoking cessation technology (smartband, smartphone app). By offering free quitting strategies, this study may help to engage more smokers into treatment, thus reducing the enormous health care costs and loss of lives associated with cigarette smoking.

SECTION VI: RESEARCH ALTERNATIVES AND ECONOMIC CONSIDERATIONS

1. Alternatives: What other alternatives are available to the study subjects outside of the research?
   Alternatives to treatment in this study are currently approved over the counter smoking cessation treatments such as the nicotine patch, nicotine gum, and nicotine lozenge. Subjects may get prescriptions from their physicians for varenicline, bupropion, the nicotine nasal spray, or the nicotine inhaler. Subjects will be recommended to use quit smoking medications while participating in this study.

2. Payments for Participation (Economic Considerations): Describe any payments that will be made to subjects, the amount and schedule of payments, and the conditions for receiving this compensation.

Study compensation will be: $10 upon completion of the zoom/online training, $20 upon completion of the second study survey, and $10 upon completion of the third study survey. At the end of the study, they will be paid $1 per day for each day of the 60-day study that they have worn their smartband for 12 waking hours (up to $60). At the end of the study, they will also be paid $10 for the end of study survey, and a $50 bonus payment if they have completed all parts of the study. **Total study payment will be up to $160** (up to $40 paid upon each survey completion, up to $120 paid at the end of the study). Please note that all study equipment (smartband, CO-monitor, saliva kit if applicable) must be returned before the final study payment. Finally, they may be invited to take part in an optional debriefing at the end of the study, for which they will be paid an additional $10. Study payments will be by amazon.com gift card.

3. Costs for Participation (Economic Considerations): Clearly describe the subject's costs associated with participation in the research, and the interventions or procedures of the study that will be provided at no cost to subjects.
   To participate in the study, participants will be required to already own a smartphone.

4. In Case of Injury: This section is required for any research involving more than minimal risk, and for minimal risk research that presents the potential for physical harm (e.g., research involving blood draws).

   a. Will medical treatment be available if research-related injury occurs? *Write here*
   b. Where and from whom may treatment be obtained? *Write here*
   c. Are there any limits to the treatment being provided? *Write here*
   d. Who will pay for this treatment? *Write here*
   e. How will the medical treatment be accessed by subjects? *Write here*

This protocol is deemed to be of minimal risk. If subjects develop a mental or physical problem as a result of involvement in this study, they will seek their own treatment independently from the study. The subject's insurance carrier will be expected to pay the costs of such treatment. No financial compensation is available for this treatment.

IMPORTANT REMINDERS

Will this study have a billable service? Yes ☐ No☒

A billable service is defined as any service rendered to a study subject that, if he/she was not on a study, would normally generate a bill from either Yale-New Haven Hospital or Yale Medical Group to the patient or the patient's insurer. The service may or may not be performed by the research staff on your study, but may be provided by professionals within either Yale-New Haven Hospital or Yale Medical Group (examples include x-rays, MRIs, CT scans, specimens sent to central labs, or specimens sent to pathology). Notes: 1. There is no distinction made whether the service is paid for by the subject or their insurance (Standard of Care) or by the study's funding mechanism (Research Sponsored). 2. This generally includes new services or orders placed in EPIC for research subjects.

If answered, "yes", this study will need to be set up in OnCore, Yale's clinical research management system, for Epic to appropriately route research related charges. Please contact oncore.support@yale.edu

Are there any procedures involved in this protocol that will be performed at YNHH or one of its affiliated entities? Yes ☐ No ☒

If Yes, please answer questions a through c and note instructions below.

a. Does your YNHH privilege delineation currently include the **specific procedure** that you will perform? Yes ☐ No ☐

b. Will you be using any new equipment or equipment that you have not used in the past for this procedure? Yes ☐ No ☐

c. Will a novel approach using existing equipment be applied? Yes ☐ No ☐

If you answered "no" to question 4a, or "yes" to question 4b or c, please contact the YNHH Department of Physician Services (688-2615) for prior approval before commencing with your research protocol.

IMPORTANT REMINDER ABOUT RESEARCH AT YNHH

Please note that if this protocol includes Yale-New Haven Hospital patients, including patients at the HRU, the Principal Investigator and any co-investigators who are physicians or mid-level practitioners (includes PAs, APRNs, psychologists and speech pathologists) who may have direct patient contact with patients on YNHH premises must have medical staff appointment and appropriate clinical privileges at YNHH. If you are uncertain whether the study personnel meet the criteria, please telephone the Physician Services Department at 203-688-2615. **By submitting this protocol as a PI, you attest that you and any co-investigator who may have patient contact has a medical staff appointment and appropriate clinical privileges at YNHH.**

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