Protocol Title: Reducing tobacco-associated lung cancer risk: A randomized clinical trial of AB-free kava

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ABSTRACT

Tobacco use is the leading cause of many preventable diseases, particularly lung cancer. Based on the national cancer data in 2020, Florida has the highest lung cancer incidence (18,150 cases) with the most deaths (10,580 deaths) among all the states in the U.S (1). Unfortunately, around 16% of Florida adults continue to smoke cigarettes due to its addictive nature and the limited success of current cessation strategies. Therefore, there is an unmet and urgent need for novel interventions to improve the success of tobacco cessation. If such an intervention can reduce tobacco-associated lung carcinogenesis, that will be more desirable. The ultimate goal of this project is to develop a safe and effective kava-based intervention to enable tobacco cessation and reduce lung cancer risk, which will improve the health of Floridians.

Building upon our promising pilot human trial results (2) in conjunction with ample compelling lab animal results (3-7), which are consistent with kava's reassuring epidemiological knowledge (8-10), this proposal will evaluate the benefits of AB-free kava in reducing tobacco use and tobacco dependence (a kava preparation free of flavokavains A and B, which are the potential hepatotoxic ingredients in kava (11), an IND enabled dietary supplement with improved safety and rigorous quality control). The secondary aims include compliance of AB-free kava among active smokers. The other exploratory aims include 1) whether AB-free kava use suppresses tobacco-induced carcinogenesis; and 2) the potential of the mechanism-based noninvasive biomarkers in precision AB-free kava intervention. The populations addressed are Floridian regular smokers – they are expected to benefit from AB-free kava use to reduce tobacco use and associated risks of various diseases, particularly lung cancer risk. Participants for this study will be recruited from University of Florida Health Family Medicine Main Street Clinic in Gainesville. Primary care settings play a critical role in tobacco-related disease screening, counseling, and early intervention, as more than 70% of smokers visit their physicians annually. This provides a great opportunity to effectively reduce smoking rates and tobacco-related diseases.

1. SCIENTIFIC RATIONALE AND BACKGROUND:

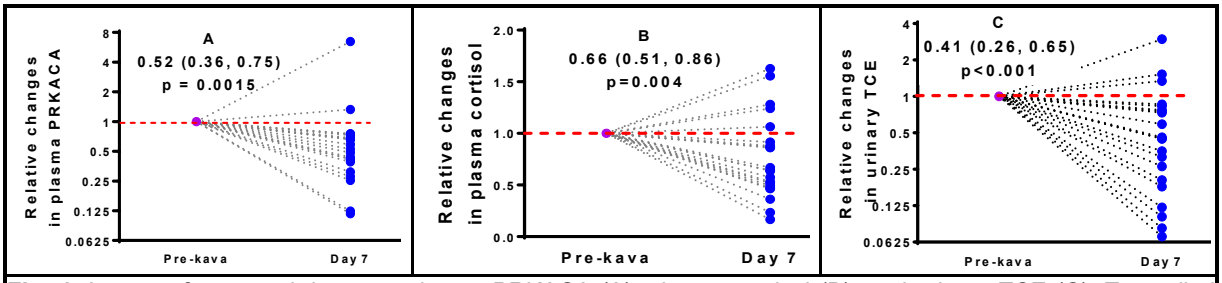


Fig. 1. Impact of one-week kava on plasma PRKACA (A), plasma cortisol (B), and urinary TCE (C). Two-tailed paired t-test was performed (n = 21). A ratio of geometric means and 95% CI presented.

Tobacco use is the leading cause of various preventable diseases in the United States and in Florida (1). Nearly half a million American adults die prematurely of tobacco exposure annually, with lung cancer accounting for 29% of such deaths. Given the limited success in current lung cancer treatment and tobacco cessation, preventing lung carcinogenesis in conjunction with reducing cigarette use may be necessary to minimize lung cancer incidence among addicted smokers. Our lab animal data (3-7) and pilot human trial results (2) indicate that kava is such a candidate, consistent with its epidemiological observations (8-10). Kava is a beverage from the South Pacific Islands that helps reduce stress and improve sleep (12). Kava has also been used to manage mild and moderate anxiety with no signs of withdraw or dependence (12). We demonstrated that kava blocked DNA damage (3-methyl adenine, 3-mA, in human urine) induced by 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (a tobacco specific lung carcinogen, known as NNK) in lab animals and smokers to prevent lung carcinogenesis (2-7). The mechanism is to enhance NNK detoxification – the increase in urinary total NNAL (2, 4, 5). Our pilot trial discovered that kava also reduced tobacco use (the reduction in 24-h urinary total nicotine equivalents – TNE, which measures the sum of the major metabolites of nicotine as an quantitative indicator of tobacco exposure) and dependence (questionnaires) among addicted smokers (2). Suppressing stress-mediated protein kinase A (PKA) activation is the potential mechanism, because PKA is elevated in smoker's brain and contributes to tobacco addiction (13). As show in Figure 1, one-week kava use among smokers resulted in a 48% reduction in plasma protein kinase cAMP-activated catalytic subunit alpha (PRKACA, the active unit of PKA) and its associated cortisol and urinary cortisol metabolites (total cortisol equivalents, TCE, which is the sum of the major cortisol metabolites as an indicator of daily overall cortisol levels). At the same time, poor quality of sleep and insomnia are known factors that contribute to the poor outcome of current pharmacological tobacco cessation interventions. Kava has been used traditionally

to help improve the quality of sleep, which may also facilitate tobacco cessation. We hypothesize that AB-free kava, an IND enabled dietary supplement with improved safety and stringent quality control, safely and effectively helps addicted smokers reduce tobacco use/dependence and enhance carcinogen clearance, minimizing lung cancer risk. The goal of this proposal is to characterize the compliance of AB-free kava use among addicted smokers, evaluate its potential to reduce tobacco use/dependence, and explore the reduction in lung carcinogenesis risk via a double-blind randomized, placebo controlled 4-week AB-free kava intervention trial. The potential of precision AB-free kava intervention will be explored as well. The sample size (20 participants, 10 in each arm with 8 expected to complete the trial) is based on the extent of tobacco use reduction (TNE) in the pilot trial (2). The AB-free kava dose regimen (3 x 75 mg daily) is based on its recommended use in human as a dietary supplement (12).

2. STUDY AIMS AND OBJECTIVES:

This study has two aims. Aim 1:To validate AB-free kava's benefits in reducing tobacco use (TNE), tobacco dependence, and lung cancer risk biomarkers. Aim 2: To document AB-free kava compliance and identify potential issues.

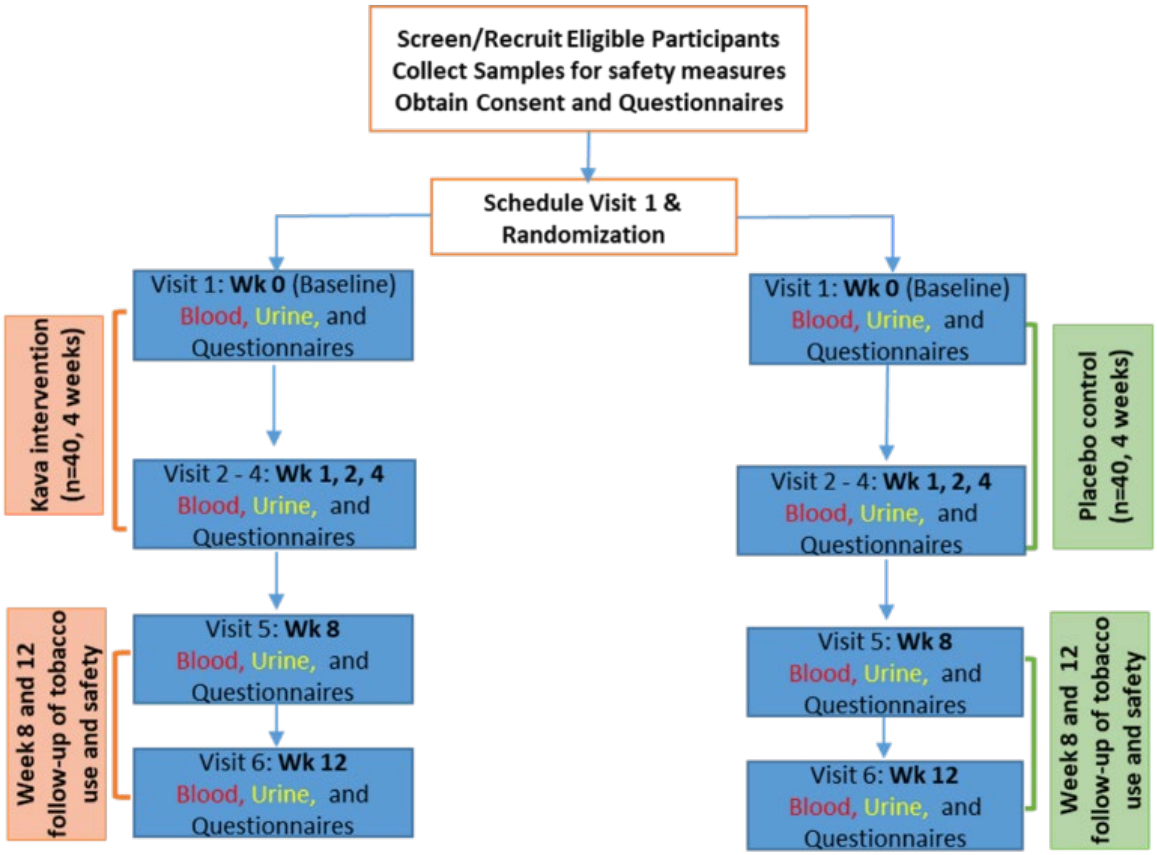
HYPOTHESIS: AB-free kava, an IND enabled dietary supplement with improved safety and stringent quality control, safely and effectively helps addicted smokers reduce tobacco use/dependence and enhance carcinogen clearance, minimizing lung cancer risk.

A. **Primary Objective:** To examine whether AB-free kava has the potential to help facilitate tobacco cessation through evaluating reduction in urinary TNE (total nicotine equivalents, which measures nicotine, cotinine, and 3-hydroxycotinine and their conjugates separately).
B. **Secondary Objective(s):** To evaluate AB-free kava compliance and identify potential issues. To examine whether AB-free kava has the potential in reducing tobacco use and tobacco dependence through analyzing tobacco cessation-related questionnaires.
C. **Exploratory Objective:** To examine whether AB-free kava has the potential to reduce lung carcinogenesis induced by tobacco specific carcinogen – NNK (reduction in urinary 3-mA and increase in urinary NNAL).

3. STUDY SCHEMA AND/OR SCHEDULE OF EVENTS:

STUDY SCHEMA

Study design of 4-week AB-free intervention, two follow-ups, and data collection.



This is a double-blind randomized placebo-controlled intervention trial. Methods of the protocols have been established in the PI and Co-I's laboratories to adequately answer the questions addressed in the objectives. The trial will require resources from the UF Community Health and Family Medicine Clinics and UF Consent2Share database to help enroll active smokers, who are otherwise healthy, to be randomized into the placebo and AB-free kava arms, being exposed for four weeks, with a total of six visits (Week 0, 1, 2, 4, 8 and 12) to evaluate the compliance and potential issues of AB-free kava use among the participant, explore the potential effect of the AB-free kava intervention on tobacco dependence, tobacco use and lung carcinogenesis biomarkers. Placebo or AB-free kava intervention are 4 weeks long with one capsule each time and three times daily approximately administered via oral at 8 AM, 1PM, and 6PM (total of 3 capsules daily). The dose of AB-free kava will be 75 mg of kavalactones per capsule. There will be no dose modification and the use will discontinue if severe adverse effect is detected, which is detailed later.

Clinic Staff members from the UF Health Family Medicine Main Street and UF Health Family Medicine Springhill clinics, under the supervision of Dr. Malaty or Dr. Orlando, will identify potential participants and briefly introduce the overall goal of the study. Once a potential participant is identified at any UF Community Health and Family Medicine location, a clinic staff member will refer the candidate to the study coordinator. The study coordinator will conduct a pre-screening phone interview to explain the study, its potential benefits/risks, and determine the eligibility. Those meeting primary inclusion/exclusion criteria and interested in participation will be scheduled for an in-person assessment. At the assessment visit, participants will be informed and will verbalize understanding that consent is voluntary and that they have the right to withdraw from the study at any time they wish without any consequences to any health care they are receiving currently or in the future. After having

their questions answered, if they would like to participate in the study, they will agree to refrain from engaging in any other smoking cessation while participating in this study and sign an informed consent form.

Once a participant signs the consent form electronically in REDCap, s/he will a breath CO test to evaluate smoking status. Blood will be screened for ALT, AST, ALP, and total bilirubin. Pregnancy test for females of childbearing potential will be done with a spot urine. Upon confirming tobacco use, normal liver function, and other criteria, qualified participants will be enrolled into this study, set up Visit 1 (typically within one week), and randomized into one of the two study arms.

Visits 1 – 6: During each of the following visits (each should take about 30-60 minutes), participants will be screened for ALT, AST, ALP, total bilirubin, breath CO test, and questionnaires administered. An additional blood sample (10 mL, onsite) and 24-h urine (Participants will be provided the collection container during each visit and will bring their urine samples to their next visit) will be used for biomarker assays. The participant then will be provided with medications and written instruction of use, supplies for the next 24-h urine collection, and scheduled for the next visit. The questionnaires include:

- Self-Reported Measure of Smoking: documenting the number of cigarettes smoked in the past 7 days.
- Fagerström Test for Nicotine Dependence (FTND): a 6-item scale measuring the level of nicotine dependency or addiction. It assesses how soon tobacco use begins each day, which cigarettes during the day a person could do without, how smokers cope in places where they cannot smoke, and how frequently and how deeply they smoke.
- Modified Cigarette Evaluation Questionnaire (mCEQ): a 12-item scale, rating several dimensions (satisfaction, psychological reward, nausea or dizziness, craving relief; enjoyment of airway sensations). It assesses the degree to which participants experience the reinforcing effect of smoking.
- Brief Questionnaire on Smoking Urges (QSU-Brief): a 10-item scale, assessing the features of craving, including the anticipation of relief of nicotine withdrawal, anticipation of positive outcomes of smoking, desire to smoke, and intention to smoke.
- Perceived Stress Scale (PSS): a 10-item scale measuring the perception of stress. It is a measure of the degree to which situations in one's life are appraised as stressful. The scale also includes a number of direct queries about current levels of experienced stress.
- Insomnia Severity Scale: a 7-item self-report questionnaire assessing the nature, severity, and impact of insomnia. Dimensions evaluated are: severity of sleep onset, sleep maintenance, and early morning awakening problems, sleep dissatisfaction, interference of sleep difficulties with daytime functioning, noticeability of sleep problems by others, and distress caused by the sleep difficulties. Because of kava's potential benefit to sleep, this questionnaire will generate preliminary data about kava's mechanism in facilitating tobacco cessation.
- Ask Suicide-Screening Questions (ASQ): consists of four yes/no questions to identify individuals that require further mental health/suicide safety assessment. According to FDA recommendation for any interventions with neurological activities, ASQ is included to assess suicide risk because of its peer-reviewed effectiveness and the lower burden on the participants.
- PATH Nicotine Exposure Questionnaire: An 18-item questionnaire collecting data on recent use of nicotine and tobacco products over the past three days. Participants report the last usage time and quantity for items like cigarettes, e-cigarettes, and smokeless tobacco, as well as other nicotine-related products. Respondents can skip questions if they choose not to answer.

At the end of the study or when a participant drops out of the study, an exit interview will be performed with open-ended questions to obtain feedbacks about the trial from the participants.

Data and biological sample collection and storage

All data (participant information, questionnaire responses, values of biological samples and others) will be stored in a REDCap database. REDCap is a HIPAA-compliant, highly-secure, and intuitive-to-use web-based application designed to capture and store data for clinical research, including questionnaire data from research participants. Data will be exported into a SAS data set for analysis. Data integrity will be evaluated using descriptive statistics (e.g., means, standard deviations, frequencies, percent, range) appropriate for measurement levels. Checks for implausible or out-of-range values, distributional forms, and missingness will be performed.

For biological samples, a research assistant will retrieve the urine and blood samples from the Clinic within 1 hour after the participant's visit and deliver to the Xing lab. The total volume of the urine sample will be recorded to the closest 10 mL. The urine samples, upon mixing well, will be split into 10 x 1 mL, 5 x 15 mL, 2 x 100 mL and stored at – 80ºC. The blood samples will be processed into plasma, buffy coat and red blood cells and stored at – 80ºC. Detailed information of these samples, including participant ID, visit #, sample information, and missed dosing or sample(s), will be recorded in the REDCap database.

4. STUDY DESIGN

To rigorously test our hypothesis and build the solid foundation for future AB-free kava translation among addicted smokers, we propose a double-blind randomized placebo-controlled longitudinal trial (4-week AB-free kava intervention vs. placebo with two follow-ups). Briefly, addicted smokers with NO intention to quit will be enrolled and randomized into two groups (those willing to quit will be referred to Tobacco Free Florida, the state tobacco cessation program). One group will take placebo capsules and the other group will take AB-free kava capsules (one capsule each time, 3 times daily, each capsule is 75 mg kavalactone) for four weeks. Safety monitoring and sample collections will be implemented at Week 0, 1, 2, 4, 8 and 12 respectively. Two follow-ups (Week 8 and 12) are designed to 1) explore the sustainable potential of AB-free kava; and 2) capture delayed adverse effects if any, both of which are critical for participants and future development. AB-free kava regimen proposed herein remains the same as in the pilot trial (2), supported by our recent pharmacokinetic results (the half-lives of the main ingredients in AB-free kava are no more than 3 hours). The 4-week AB-free kava exposure is expected to provide sufficient data about AB-free kava's compliance, efficacy and safety while minimizing potential risks among the participants. At the end of Week 12, all enrolled participants will be recommended to Tobacco Free Florida to maximize the chance of tobacco cessation.

Florida Department of Health has funded the proposed clinical trial via a 5-year clinical trial grant through the James Esther King Mechanism. The methods, protocols, and expertise are all in place in the PI and Co-I's research group. The proposed objectives are expected to be achievable in the 5-year funding period. The safety of the participants will be closely monitored that the intervention will stop following the rules below:

1. Participants will be assessed for ALT, AST, ALP and total bilirubin using blood samples collected during the visits at baseline, week 1, 2, 4, 8 and 12 to monitor potential acute or delayed hepatotoxic risk. During the visits at baseline, week 1, and 2, the participant will receive the drug supplies for 1 week (at baseline), 1 week (at week 1), and 2 weeks (at week 2). The ALT, AST, ALP and total bilirubin test results will be available to the research coordinator within 24 hours after the blood sample collection and the participant will be notified of the results immediately after they become available if the levels are out of the range as defined below. The patient will be instructed to stop taking the study drug if they are not in contact with the clinic regarding their lab results within 24 hours of the blood draw. During the period of time between blood sampling and lab results, which is within 24 hours, the participant will continue to take the medication as scheduled. This is the standard protocol for the clinical evaluation of standard therapeutics, even those with high risk of hepatotoxicity. Given the very low risk of hepatotoxicity reported for kava (< 0.3 case per 10^6 dosages), the protocol has built in adequate measures to minimize the potential risk associated with kava use without significantly compromising the goal of the trial. Participants, whose ALT, AST, ALP or total bilirubin increases > 3 x the upper limit of normal (ULN) but ≤ 5 x ULN, will retest after 48 to 72 hours. The patient will continue taking the study drug during this time. If ALT, AST, ALP or total bilirubin increases to >5 x ULN, the study drug will be discontinued and participant referred for further clinical evaluation and treatment. For any increase in ALT, AST, ALP or total bilirubin >3 x ULN associated with fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever and/or rash, study drug will be discontinued and participant referred for further clinical evaluation.

5. SELECTION OF SUBJECTS

Justification for UF Health Family Medicine Main Street and Springhill Clinics a) Over 1700 adult smokers visited these clinics last year for annual checkups, >50% of whom smoke at least 10 cigarette/day. Although our exclusion criteria is stringent (detailed below), we expect at least 15 – 20% recruitment rate given the high success to recruit participants in family clinics for tobacco trials; b) successful track record of recruiting smokers to support clinical research, including collaborations between Drs. Salloum and Malaty (co-Is), who have previously recruited

120 adult smokers from the same clinic in 4.5 months (NCT03836573); c) electronic health record information of patients in the clinics will help identify eligible participants – those without previous liver diseases; and d) most importantly, the clinical expertise, resources, and facilities will minimize potential adverse effects in this trial.

There are no additional requirements with respect to gender, employment, geographical, language, or other factors.

Our targeted accrual goal is 20 active smokers. Based on our previous enrolling experience at the UF Health and Family Medicine Main Street Clinic and our rather stringent inclusion/exclusion criteria, the enrollment is expected to be 3 – 3.5 years with the duration of each participant to be 13 – 14 weeks.

The participants will be referred to the study team through any of the UF Community Health and Family Medicine clinic. Potential participants will be referred to either the Main Street or Springhill clinics, under the supervision of Dr. John Malaty or Dr. Frank Orlando, who will confirm potential participants and briefly explain the study. Once a potential participant is identified, the clinic staff will refer the candidate to the study coordinator. Participants will also be referred to the study team through the UF Consent2Share program.

Justification for excluding pregnant women. Given the proposed mechanism of AB-free kava to facilitate the reduction of tobacco use through the modulation of stress, pregnant women will be excluded from this study because pregnancy is expected to introduce significant changes on mental status and hormone physiology. Such variations are expected to compromise the sample size justification and therefore the primary goal of this early-phase clinical study.

Total Number of Subjects (should be total of a + b): **20**
Total Number of Subjects (affiliate sites, if applicable): **not applicable**
Total Number of Subjects (UF site): **20**

Key Inclusion Criteria:

A) adults aged 21 years or above (legal age for smoking in the U.S.);
B) self-reported smoking at least 5 cigarette/day for the past year with no intention to quit at time of screening visit;
C) expired carbon monoxide level of more than 8 ppm at recruitment;
D) willingness to participate in the proposed study, as indicated by signed informed consent;
E) access to a functional telephone;
F) expected presence in the study's geographical area for the next 4 months;
G) not currently enrolled in any smoking cessation programs per self-report; and
H) for female subjects of childbearing potential will be required to practice acceptable methods of birth control (the acceptable methods of birth control include birth control pills, Birth Control Shot, Birth Control Implant, IUD, Diaphragm, and cervical cap).

Key Exclusion Criteria <u>(any of the following)</u>:

A) history of active cancer (other than non-melanoma skin cancer) within the past 2 years;
B) diagnosed with liver dysfunction or with previous liver diseases;
C) levels of ALT, AST, ALP or total bilirubin over limit of normal (ULN) range at prescreen;
D) inability to refrain from acetaminophen, alcohol (no more than one drink daily via self-report);
E) are pregnant or nursing (lactating) or of childbearing age planning to become pregnant or unwilling to use adequate contraception during the study;
F) participant answered "Yes" to any of the ASQ questions 1 through 3, or refuses to answer all of the questions. If subject answers 'Yes' to question 4 but the most recent suicide attempt took place >12 months from screening visit then subject is still eligible.

6. STUDY PROCEDURES

<u>Enrollment and study procedures</u> Permission to conduct this study will be obtained from the UF IRB prior to start. Subjects can be recruited from any UF Community Health and Family Medicine location. Clinic Staff members from the UF Health Family Medicine Main Street and Springhill clinics will identify potential participants and briefly explain the study. Once a potential participant is identified, clinic staff members will refer the candidate to the study coordinator. Additional subjects may be referred to the study coordinator via the UF Consent2Share database. The study coordinator will conduct a pre-screening phone interview to determine the eligibility. Those meeting primary inclusion/exclusion criteria and interested in participation will be scheduled for an in-person assessment. At the

assessment visit, participants will be informed and will verbalize understanding that consent is voluntary and that they have the right to withdraw from the study at any time they wish without any consequences to any health care they are receiving currently or in the future. After having their questions answered, if they would like to participate in the study, they will agree to refrain from engaging in any other smoking cessation while participating in this study and sign an informed consent form.

Once a participant signs the consent form electronically in REDCap, the participant will complete breath CO test to evaluate smoking status. The participant will be given a screening questionnaire by study staff to document smoking status, no desire to quit, and other self-report items to confirm eligibility. Given the common experience of smokers to fluctuate whether they want to quit smoking or not, only self-reported desire (or lack of) during this screening process will be used to determine eligibility. Screening procedures performed per Standard of Care within the screening window can be used even if prior to consent. Upon confirming tobacco use, normal liver function, no alcohol abuse (via self-report and questionnaires), qualified participants will set up Visit 1 (typically within one week), and be randomized into one of the two study arms. During each of the following visits, participant liver function will continue to be monitored with blood tests, a breath CO test, and questionnaires. An additional blood sample (10 mL) and 24-h urine (collected the day before the visit, patients will be provided collection container during each visit) will be used for biomarker assays. The participant then will be provided with medications, written instruction of use, and supplies for the next 24-h urine collection, and scheduled for the next visit. The questionnaires to be administered have been previously listed in the Study Schema and/or Schedule of events section.

Randomization Participants who meet eligibility criteria will be randomized to the AB-free kava or the placebo group using a 1:1 allocation scheme, stratified by age, gender and heavy/light consumption of cigarettes per day. IDS randomizes the subject based on the criteria entered with the first Order placed in EPIC for Study IP. IDS does not provide any documentation to the study team that randomization occurred. Upon completion of all proposed analyses, IDS will provide the randomization record to the PI, Co-Is and Dr. Lin to un-blind assignment. As IDS will operate independently of the study team, the study will be a double-blind trial.

Intervention AB-free kava and placebo will be obtained from Thorne Research Inc.. Chemistry, Manufacturing and Controls (CMC) data have been reviewed by Food and Drug Administration (FDA) with an enabled Investigational New Drug (IND, #142838) for a trial among patients with generalized anxiety disorder (GAD). The IND for this study has been approved (IND #157256). Such AB-free kava capsules have been analyzed in-house as well for its abundance of kavalactones and lack of flavokavains A and B by our established LC-MS/MS method (14). AB-free kava or placebo will be administered as follows: one capsule by mouth ideally with meals three times a day (around 8:00 a.m., 1:00 p.m., and 6:00 p.m.) for 28 days. This will result in a daily dose of 225 mg kavalactones for AB-free kava group participants. If a dose is missed, participant will not double the dose at the next scheduled time but document the missed dose and return the missed dose at the next visit.

Retention strategies and incentives The study team has an excellent history of retaining clinical trial participants. We will always use respectful, empathetic communication and be considerate of participants' time when scheduling research activities. Compliance and retention will be maximized via the following methods: a) close monitoring during participation; b) a reminder phone call to confirm study visits; c) 24/7 access to the study team during participation; and d) establishing appropriate rapport such that the participant feels motivated to return. Participant will also receive a gift card for each visit as compensation. These strategies should minimize missing data and improve data validity.

Preparing, dispensing and recording study supplements by IDS Supplies for each participant will be prepared by IDS following randomization. Instructions on use and storage will be provided in writing. Participants will be asked to keep track of missed dose. Unused materials will be returned at the next visit, recorded and destroyed by IDS. IDS will maintain a Study Drug Accountability log for each participant, which will record participant ID, randomization code, medication ID, dates of medication dispensed, returned, missed dose, number of capsules returned, and medication destruction.

Data and biological sample collection and storage All data (participant information, questionnaire responses, values of biological samples and others) will be stored in a REDCap database. REDCap is a HIPAA-compliant, highly-secure, and intuitive-to-use web-based application designed to capture and store data for clinical research, including questionnaire data from research participants. Data will be exported as an R-compatible data set for statistical analysis. Data integrity will be evaluated using descriptive statistics (e.g., means, standard deviations, frequencies, percent, range) appropriate for measurement levels. Checks for implausible or out-of-range values, distributional forms, and missingness will be performed.

For biological samples, a research assistant will retrieve the urine and blood samples from the Clinic within 1 hour after the participant's visit and deliver to the Xing lab. The total volume of the urine sample will be recorded to the closest 10 mL. The urine samples will be split into 5 x 15 mL and stored at – 80ºC. The blood samples will be processed into plasma, buffy coat and red blood cells and stored at – 80ºC. Detailed information of these samples, including participant ID, visit #, sample information, and missed dosing or sample(s), will be recorded in the REDCap database.

Minimizing potential risk to confidentiality: Any concerns related to the intervention and privacy will be shared with the PI and every effort will be made to protect the participants' information during the study. All study personnel are accustomed to maintaining and ensuring patient confidentiality in the course of their work. In addition, all study personnel are highly trained in research procedures and in issues regarding protection of participants' rights and privacy. All members of the research team, including the PI, coinvestigators, study coordinator, data collectors, research assistants, data manager, and all students associated with the project will complete UF-mandated human subject training prior to study commencement. Participants' identities will be protected through the following measures: consent forms will be stored behind a locked door and in a locked filing cabinet accessible only by the PI, and all identifying information will be stored in a separate, secured location from data that is collected during the study. Access to locked files will be restricted to essential personnel only. In addition to consent and identification files that are secured, all data files will be coded in a manner that makes identification of the participants extremely unlikely. Indeed, participants will be given a numerical ID code to ensure that inadvertent or unauthorized identification does not occur. Data will receive additional layers of security because the whole building, floor, and office in which locked records are maintained have restricted, keyed access. The anonymous codes assigned to participants will be verified and maintained by Dr.Salloum throughout the study, and codes with names will be provided only to meet federal guidelines applicable to the facility. Data will be entered into a REDCap database developed for the project. REDCap (Research Electronic Data Capture) is a secure, HIPAA-aligned web-based application designed to support traditional case report form data capture. REDCap's automated export procedure will be utilized to export data into a SAS data set for analysis. Our research coordinator will conduct the screening of potential participants working closely with the clinical staff. The research coordinator will meet with Dr. Salloum weekly to discuss study progress.

Environment Assessment (EA): An Environmental Assessment is not required because the action requested qualifies for a categorical exclusion per 21 CFR 25.31(e). To the applicant's knowledge, no extraordinary circumstances exist per 21 CFR 25.15(d).

7. POSSIBLE DISCOMFORTS AND RISKS

Possible discomforts and risks from taking kava supplement are minimal. Preliminary data from a previous human study did not report any adverse events due to the consumption of kava supplementation. Because there is a potential for kava to affect the function of the liver through drug-herb interactions (<0.3 cases per million dosages), we will exclude any subjects with known liver conditions as described in the inclusion criteria and will monitor liver function during and after participants are receiving the intervention. AB-free kava (a kava preparation free of flavokavains A and B, the potential hepatotoxic ingredients in kava (11)) will be used the study as well, which is expected to have an improved safety profile. In the event that serum liver enzymes become elevated (3 times the normal range, which is considered as mild elevation clinically), participants will be notified immediately and retested in the next 48 – 72 hours. If increases to >5 x ULN, the study drug will be discontinued and participant referred for further clinical evaluation and treatment. For any increase in ALT, AST, ALP or total bilirubin >3 x ULN associated with fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever and/or rash, the study drug will be discontinued and participant referred for further clinical evaluation and treatment. No severe adverse effects have been detected in the pilot kava trial. There is minimal risk associated with blood draws, which will be performed by certified professionals. Similarly, there are potential risks to confidentiality for participants in this study. However, these risks are minimal given our procedures to protect against these risks. No other discomforts and risks (physical, psychological, social, and/or economic), study participants are expected to encounter. Given kava's potential neurological functions, we have built in an Ask Suicide-Screening Questions (ASQ) form to assess the suicide risk. This questionnaire will be evaluated in real time by a trained Study Coordinator who can refer the patient to mental services if needed. Should such an emergency arise (statement or demonstration of active suicidal ideation), standard of care clinic procedures will be followed. Specifically, Alachua County Crisis Center would be called (352-264-6789) to have the patient evaluated in clinic (they send a staff member to clinic to see the patient) or the patient would be sent directly to a

psychiatric facility (Vista or Meridian) for further evaluation and management either voluntarily or under a Baker Act.. Additionally, all patients will be provided with resources for mental health help. The following numbers will be provided to patients in the ICF as well as upon request, UF psychiatry clinical sites (352) 265-4357., the Alachua County Crisis Center (352) 264-6789, and the National Suicide Hotline 1-800-784-2433. In addition, kava use may result in sedation that the participant should not operate heavy instruments and should drive with care within 2 h after AB-free kava use, until they know how it affects them although such a risk is extremely low at the proposed dosage regimen. There are no potential financial risks that study participants may incur given the trial is free of charge to participants with all supplies provided and incentives are provided as well. Additionally, our clinical team has ample experience to protect against or minimize potential unexpected discomforts and risks.

8. POSSIBLE BENEFITS

There are several potential benefits from the study. AB-free kava may provide individuals randomized to the AB-free kava group a decrease in the urge to smoke, thereby making it an effective smoking cessation treatment. It may reduce levels of NNAL and DNA damage caused by tobacco carcinogens, which would indicate reduced carcinogenesis. This could be an effective, low-cost strategy to help people quit smoking and potentially reduce lung cancer risk. The risks for this study, as discussed above, are minimal and are far outweighed by the potential benefits to be gained regarding smoking cessation and the reduced risk of lung cancer.

Regardless of the findings, this study will make a significant contribution to the literature in the field of supportive care. Indeed, it will fill a vital gap in the literature regarding the ability of kava to reduce the urge to smoke as well as carcinogens in the body. In addition, this study will provide data for manuscripts that can be published in peer-reviewed, high impact journals, as well as manuscripts that can be published in lay journals for the public. Finally, this study will yield information that the investigators will disseminate at local, regional, state, and national meetings and will serve as the basis for conducting a follow-up, Phase III randomized control trial. In all presentations, we will use necessary scientific language about inclusion/exclusion criteria of the trial and about potential interaction with other widely used medications (i.e., acetaminophen) to minimize the risk of abuse.

9. ADVERSE EVENTS/UNANTICIPATED PROBLEMS

To minimize and closely monitor any potential Adverse Events/Unanticipated Problems, liver function tests will be monitored during the treatment period with 4 and 8-week follow-ups, which will be sufficient even based on kava's reported hepatotoxic cases (15). Specifically, participants will be asked to control alcohol use and refrain from products containing acetaminophen through the study period. They will be provided with a reference list of medications that contain acetaminophen. ALT, AST, ALP, and total bilirubin will be assessed at every visit to ensure any adverse effects/risks identified and addressed. Alcohol use will be assed via questionnaires (self-report). The AE collection period will start at Visit 1 when the first pills are dispensed to the participant and end at Week 12 follow-up visit. In addition to all serious adverse events (grade III and above), only non-serious adverse events (less than grade III) that are possible, probable, or definitely related will be reported into the study REDCap. Dr. Malaty or Dr. Orlando will supervise liver screening and safety monitoring. Participants with an increase in liver biochemistry will be referred to clinical services at UF for further evaluation to minimize the risk with plan detailed below. Dr. Malaty or Dr. Orlando, in consultation with Dr. Firpi (co-I and a hepatologist with clinical expertise in liver safety monitoring), will report any relevant adverse events to the Institutional Review Board (IRB) that meet the boards reporting requirements.

10. STATISTICAL ANALYSIS PLAN

Sample size determination: the sample size was estimated based on urinary TNE data from our pilot trial (urinary TNE is a primary endpoint, indicative of the amount of tobacco use). We recalculated the power based on a longitudinal study design. After accounting for the within-subject correlation in calculating the pooled standard deviation (SD) and assuming the placebo group exhibits at most 15% of the treatment effect, the standardized effect size (mean difference / pooled SD) is 1.03. A sample size of 16 participants (8 per group) completing the study achieves 82% power to detect this effect size with six repeated measurements (Week 0, 1, 2, 4, 8 and 12) using linear mixed models with AR(1) covariance structure when the within-subject correlation is 0.78 (estimated from pilot data) and a one-sided $\alpha = 0.05$. The power analysis is performed using PASS software.

Data analysis plan:

Principle All data (questionnaires and biomarkers) will be checked for out-of-range values and normality. Decisions regarding parametric vs nonparametric statistics and data transformation will be based on such results. Participants who received at least one dose of AB-free kava treatment or placebo, and have at least one more visit beyond the baseline visit will be considered as evaluable.

Missing data consideration We expect to have three scenarios for participants with respect to missing data. (1) Participants complete all visits and have no missing outcomes. They will be included in the statistical analysis. (2) Some participants may not complete all visits, but have outcomes for at least one visit after the baseline visit. These participants will be included in the statistical analysis as well. The missing outcomes will be handled by linear mixed models for longitudinal data analysis. (3) Participants do not complete the first two visits after randomization. They will be excluded from data analysis and we will replace these participants (also see replacement plan section). An enrolled participant will be replaced if s/he (i) is not involved in the baseline visit, or (ii) is only involved in the baseline visit not in any of the next five visits. Such cases are expected to be no more than 20%.

Account for spurious data: All data (questionnaires and biomarkers) will be checked for out-of-range values and normality. If any spurious data (outliers) were identified, we will fit nonparametric statistical models to assess the robustness of our primary parametric data analysis.

Replacement Plan If a participant for any reason leaves the study, the study team will recruit a new participant to replace the study subject that is no longer in the study.

Primary Endpoints – Tobacco use (urinary TNE, (total nicotine equivalents))

Longitudinal data analysis To study the relationship between longitudinal outcomes and treatment effect, we will fit linear mixed models (LMM) with subject specific random effects to account for within subject correlation, using R software *mmrm* package. LMM can accommodate missing outcomes if they are missing at random. *Baseline outcomes and covariates including age, sex, race, smoking status will be adjusted to account for confounding effects.* Past COVID-19 status may also be a covariate if there are enough cases. Urinary TNE will be used to describe how the statistical models test our working hypotheses.

Hypothesis 1: active AB-free kava treatment (week 0 – week 4) is effective in reducing TNE as compared to the placebo group. To test this hypothesis, we will fit the following linear mixed model:

$$y_{it} = \mu + \alpha_i + [\eta + \beta \mathbb{I}(z_i = 1)]t + \sum_{l=0}^{L} \gamma_l x_{il} + \varepsilon_{it}, \alpha_i \sim N(0, \sigma_0^2), \varepsilon_{it} \sim N(0, \sigma^2) \quad (1)$$

where y_{it} is the outcome variable (e.g., TNE) for subject i and week t ($0 \le t \le 4$ weeks); μ is the intercept term; $\alpha_i \sim N(0, \sigma_0^2)$ is the random effect with variance term σ_0^2 for subject i; z_i is the treatment indicator with $z_i = 0$ for the placebo group and $z_i = 1$ for the AB-free kava group; η is the slope of time effect of the placebo group; β is the additional slope of the treatment effect (AB-free kava group compared to placebo group) and $\mathbb{I}(.)$ is the indicator function which equals to 1 if the argument inside $(.)$ is true and equals 0 otherwise; x_{il} is the l^{th} covariates for subject i with $l = 0$ for baseline level of the outcome measurements (e.g. baseline TNE) and $l = 1,2, \dots, L$ for L covariates (e.g., age, sex, race, smoking history, etc.); $\varepsilon_{ik} \sim N(0, \sigma^2)$ is the error term with variance σ^2. In Equation (1), β is the additional slope of active AB-free kava effect during week 0 to week 4 compared to the placebo group; we will perform the statistical hypothesis testing (H_0: $\beta = 0$) to provide its p-value, point estimate and confidence interval. A significant p-value will indicate that the AB-free kava treatment significantly reduces TNE during week 0 through week 4 compared to the placebo group. Equation (1) only considers a random intercept, which allows the baseline level of the outcome measurement to be different. We will further incorporate random slope terms in Equation (1), if the slopes of the linear trajectories vary among different individuals, which is likely. In addition, if we observe that the trajectory of AB-free kava's effect through weeks 0, 1, 2, and 4 is not linear, we will consider to use the observations at week 0 and week 4 to test **Hypothesis 1**. The following linear model will be fitted:

$$\Delta y_i = \mu + \mathbb{I}(z_i = 1) \times \theta + \sum_{l=0}^{L} \gamma_l x_{il} + \varepsilon_i, \varepsilon_i \sim N(0, \sigma^2) \quad (2)$$

where Δy_i is the 4-week TNE change from week 0 for subject i; μ is the intercept; θ is the cumulative active AB-free kava effect in 4 weeks compared to the placebo group. We will perform the statistical hypothesis testing and provide point and confidence interval estimates of the efficacy treatment effect θ.

Hypothesis 2: AB-free kava has a sustainable effect in reducing TNE in week 4 – week 12. The knowledge about AB-free kava's sustainable effect is critical for its future development and practice. We will test whether the

AB-free kava effect (week 0 – week 4) can be extended to the follow-up period week 4 – week 12, when AB-free kava treatment is absent. The following two sub-hypotheses will be examined:

Hypothesis 2a: AB-free kava's effect will sustain to the follow-up period. To test this hypothesis, we will only consider the AB-free kava treatment arm with $4 \leq t \leq 12$ weeks. We will fit the following linear mixed model:

$$y_{it} = \mu + \alpha_i + \beta_1 \mathbb{I}(t = 8) + \beta_2 \mathbb{I}(t = 12) + \sum_{l=0}^{L} \gamma_l x_{il} + \varepsilon_{it}, \alpha_i \sim N(0, \sigma_0^2), \varepsilon_{it} \sim N(0, \sigma^2) \quad (3)$$

where μ is the AB-free kava treatment effect at week 4; β_1 is the AB-free kava treatment effect at week 8 compared to week 4; β_2 is the AB-free kava treatment effect at week 12 compared to week 4; the rest of the parameters have the same interpretation as Equation (1). In Equation (3), we will perform the statistical hypothesis testing (H_0: $\beta_1 \leq 0$ vs H_A: $\beta_1 > 0$, and H_0: $\beta_2 \leq 0$ vs H_A: $\beta_2 > 0$). Rejecting the null hypothesis will imply $\beta_1 > 0$ or $\beta_2 > 0$, which indicates that the AB-free kava effect is not sustainable. In other words, TNE level will go up and the participants likely relapse. Failing to reject the null hypothesis will imply that the TNE level stays steady and the AB-free kava treatment effect likely sustains through week 8 and week 12. We will provide their p-value, point estimates and confidence intervals.

Hypothesis 2b: the extended AB-free kava effect is superior to placebo. To evaluate this hypothesis, we will directly apply Equation (1) in **Hypothesis 1**, but treat week 4 as baseline, and week 12 as follow-up. Under this scenario, β is the slope of the extended AB-free kava effect (week 4 – 12) compared to the placebo group. We will perform the statistical hypothesis testing (H_0: $\beta = 0$) to provide its p-value, point estimate and confidence interval. A significant p-value will indicate that the extended AB-free kava effect significantly reduces TNE during the follow-up period (week 4 through week 12) compared to the placebo group, indicating AB-free kava's sustainable effect superior to placebo.

Secondary Endpoints for Tobacco Cessation and Lung Cancer Risk – Tobacco dependence (questionnaires). For each item and total score of each questionnaire, the mean and 95% confidence interval (CI), median (range), will be estimated at each timepoint, accompanied by graphical illustrations. LMM will be applied to compare the total score between kava and placebo groups across all timepoints.

Secondary Endpoint – Compliance Such information is critical for data interpretation and future clinical trial improvement. We will evaluate trial compliance in three ways as we have done in the pilot trial (2): **i**) self-report of missed doses from participant diary; **ii**) returned pill counts by IDS pharmacy; and **iii**) urinary detection of dihydromethysticin (DHM) in participants during AB-free kava exposure since DHM is kava-specific (14). In combination with the exit interview, the results will provide knowledge of the feasibility of AB-free kava use and potential issues among smokers with current treatment regimen. Compliance data will be summarized using mean (SD) and median (range) for continuous outcomes, and frequency (%) for categorical outcomes.

Exploratory Endpoints - lung carcinogenesis risk biomarkers (urinary 3-mA and urinary NNAL), and mechanism-based biomarkers (plasma PRKACA, plasma cortisol, and urinary TCE (total cortisol equivalents)). The longitudinal measurements of these exploratory biomarkers will be analyzed using the same hypotheses and LMM approach as applied to TNE.

Exploratory hypothesis 3: tobacco reduction by AB-free kava is potentially mediated via reductions in plasma PRKACA, cortisol or urinary TCE. Our pilot data suggested that smokers with higher baseline levels of cortisol appeared to have more reductions in TNE upon AB-free kava use (Fig. 2A) while the extents of reduction in TNE correlate positively with the reductions in plasma cortisol (Fig. 2B). Although the difference and correlation were not statistically significant, these results support the potential association between stress reduction and tobacco use reduction. We therefore hypothesize that changes in plasma PRKACA, plasma cortisol or urinary TCE are potential mediators for the effect of AB-free kava in reducing TNE. To test this hypothesis, we will perform mediation analysis, where TNE reduction is the outcome variable, AB-free kava intervention is the

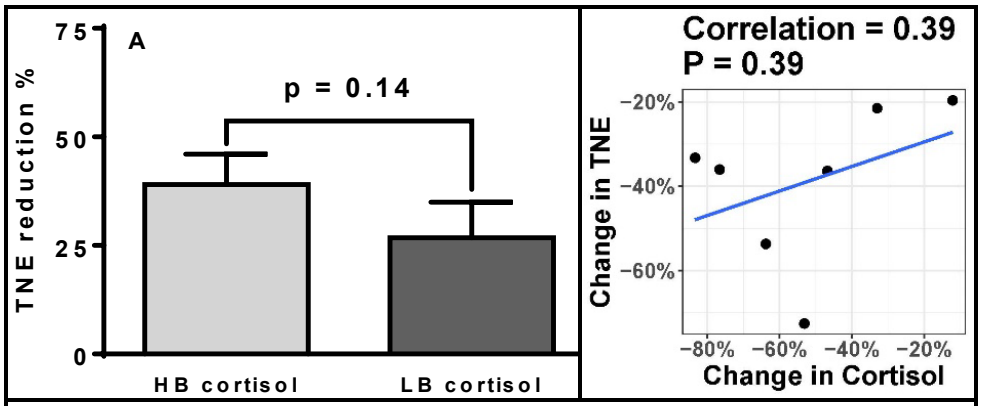


Fig. 2. Reduction of TNE among high baseline (HB) and low baseline (LB) TCE subgroups via one-tailed t-test (A) and correlation of TNE reduction and plasma cortisol reduction among HB cortisol subgroup (B).

predictor, plasma PRKACA, cortisol or urinary TCE is the mediator, adjusting for age, sex, race, and smoking status as covariates. The direct effects, indirect effects, and mediation proportion will be determined using the R *mediation* package. Their p-values and 95% confidence intervals will be reported. Such hypothesis, if tested positive, will provide mechanistic insight – whether AB-free kava may induce TNE reduction via relieving stress.

Exploratory hypothesis 4: baseline levels of plasma cortisol, PRKACA or urinary TCE can benchmark the efficacy of AB-free kava treatment (precision intervention potential). To test this hypothesis, we will fit linear mixed models within the AB-free kava group, where the repeated measurement of TNE are the outcome variables, baseline level of plasma cortisol, PRKACA or urinary TCE is the predictor, assuming subject specific random effect, and adjusting for the covariates mentioned previously. If these baseline biomarkers are significant predictors of TNE reduction, we will further dichotomize participants into high/low groups using median (or tertile/quartile), and examine AB-free kava efficacy based on groups determined by these biomarkers. If this hypothesis is tested positive, AB-free kava has the potential of precision intervention with these biomarkers to identify those who will benefit the most of AB-free kava use.

11. STUDY MONITORING

Data and Safety Monitoring Plan Once a participant is enrolled, continuous monitoring will be conducted by Drs. Salloum and Firpi (PI and Co-Is), in conjunction with other investigators as well as IRB. Any serious adverse events as well as unanticipated problems involving risks to participants or others, will be reported to IRB, FDOH, and FDA. Our monitoring plan includes the following measures:

1. Monitor adverse events, study progression, and data quality issues; consider factors external to the study when interpreting data, such as new scientific or therapeutic developments that may have an effect on the safety of the participants or the ethics of the study; and maintain confidentiality during all phases of the trial.
2. Participants will be assessed for ALT, AST, ALP and total bilirubin at baseline, week 1, 2, 4, 8 and 12 to monitor potential acute or delayed hepatotoxic risk. Participants, whose ALT, AST, ALP or total bilirubin increases > 3 x the upper limit of normal (ULN) but ≤ 5 x ULN, will retest after 48 to 72 hours. If increases to >5 x ULN, the study drug will be discontinued and participant referred for further clinical evaluation and treatment. For any increase in ALT, AST, ALP or total bilirubin >3 x ULN associated with fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever and/or rash, study drug will be discontinued and participant referred for further clinical evaluation.
3. The study will undergo regular audits by a Data Integrity and Safety Committee (details in Section 12).

12. DATA INTEGRITY AND OVERSIGHT

Per UF IRB requirements, the PI will be personally responsible for conducting and supervising the conduct of human subjects research by “protecting the rights, safety, and welfare of subjects under the investigator’s care.” The PI will also ensure that all the research conducted is done so in an ethical manner and in accordance with all federal, state, and local laws and regulations, institutional policies, and the requirements of the IRB. The PI has voluntarily accepted these responsibilities and will fully comply with these requirements, as outlined in the UFHCC Guidance: Principal Investigator Responsibilities and Oversight.

The PI will be primarily responsible for continuous monitoring of adverse events, unanticipated problems, protocol violations, and other immediate protocol issues. The PI or their designee will collect information on subjects enrolled through the use of electronic or paper source documents, CRFs, and Informed Consent forms.

The PI will be responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents will be completed in a neat, legible manner to ensure accurate interpretation of data. The study team will maintain adequate case histories of study subjects, including accurate case report forms (CRFs), and source documentation.

Data Integrity and Safety Committee (DISC). This protocol will be reviewed and monitored by the University of Florida Health Cancer Center Data Integrity and Safety Committee (UFHCC DISC) in accordance with their policies and procedures. They will review and monitor study progress, toxicity, safety and other data from this trial. Questions about subject safety or protocol performance will be addressed with the sponsor-investigator, statistician

and study team members. Should any major concerns arise, the DISC will offer recommendations regarding whether or not to suspend the trial.

UFHCC DISC data and safety monitoring activities include:

- Review of clinical trial conducted for progress and safety
- Review of all adverse events requiring expedited reporting as defined in the protocol
- Review of reports generated by data quality control review process
- Notification of the sponsor-investigator of recommended action
- Notification of sites coordinated by the UFHCC of adverse events requiring expedited reporting and subsequent committee recommendations for study modifications

In compliance with the UFHCC data and safety monitoring plan, the PI will provide a Data Integrity and Safety Committee Report to DISC at the predetermined timelines for the level of risk category assigned during the initial SRMC CCPSP (Scientific Review and Monitoring Committee Cancer Control and Population Sciences Panel) review, which occurs prior to initial IRB approval.

UFHCC investigator-initiated protocols will be classified into one of the following categories of risk by the SRMC CCPSP (see *SRMC manual* for further details):

Level 1 – **Low risk** Investigator Initiated interventional trials.
Level 2 – **Moderate risk** Investigator Initiated or externally sponsored interventional (such as drug, biologic or device) trials using FDA approved or commercially available compounds or interventions.
Level 3 – High **risk** Investigator Initiated or externally sponsored interventional trials (such as investigator-sponsored INDs, Phase I trials, studies requiring biosafety approval, or other areas that may be designated by NIH as high risk).
Level 4 – Complex trials involving **very high risk** to subjects and a high level of complexity such as first in human or gene transfer studies.

The risk level assigned by the SRMC CCPSP will determine the appropriate level of DISC monitoring required, with increased monitoring required for higher-risk trials.

13. DATA MANAGEMENT

Data collection for the trial will be managed through REDCap and stored on secure UF servers. Questionnaire data forms will be subject to computerized range and consistency checks. Biological data will be subject to computerized range and consistency checks as well. Initial examination of data will include descriptive statistics, frequency distributions, and histograms in order to identify outliers, missing data and check data source adequacy. This process will be supervised jointly by the PI and the lead statistician. Data will be periodically converted to SAS and R data types. Any entry error and/or inconsistency will be discussed during meetings with the study team. Quarterly statistical summaries and progress reports will be generated by the statistician for review by all investigators. To ensure participant confidentiality, all personal identifiers will be expunged from the data set.

14. CONFLICT OF INTEREST

The funded grant will evaluate AB-free kava's potential to help smokers reduce tobacco use and risk of lung cancer. The AB-free kava product to be evaluated is developed by Thorne, based on the IPs owned by Kuality Herbceutics (KH). KH has an estimated value of $400,000 on the basis of the IP and the investment to date, which is to support IP protection. There is no profit or product from KH yet. Chengguo Xing (the PI of this grant) owns 55% of the stock of KH. He also provides consultation to KH for its strategy on development.

Describe any conflict of interest relevant to this protocol. If none to note, please note “Not applicable”.

15. REFERENCES

1. Prevention CfDCa: Centers for Disease Control and Prevention. 2018.

2. Wang YN, S.; Tessier, K.; Strayer, L.; Upadhyaya, P.; Hu, Q.; Kingston, R.; Salloum, R. G.; Lu, J.; Hecht, S.S.; Hatsukami, D.; Fujioka, N.; Xing, C. The Impact of One-week Dietary Supplementation with Kava on Biomarkers of Tobacco Use and Nitrosamine-based Carcinogenesis Risk among Active Smokers. Cancer Prev Res. 2020;13:483-492.

3. Leitzman P, Narayanapillai SC, Balbo S, Zhou B, Upadhyaya P, Shaik AA, O'Sullivan MG, Hecht SS, Lu J, Xing C. Kava blocks 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone-induced lung tumorigenesis in association with reducing O6-methylguanine DNA adduct in A/J mice. Cancer Prev Res. 2014;7:86-96.

4. Narayanapillai SC, von Weymarn LB, Carmella SG, Leitzman P, Paladino J, Upadhyaya P, Hecht SS, Murphy SE, Xing C. Dietary Dihydromethysticin Increases Glucuronidation of 4-(Methylnitrosamino)-1-(3-Pyridyl)-1-Butanol in A/J Mice, Potentially Enhancing Its Detoxification. Drug metabolism and disposition: the biological fate of chemicals. 2016;44:422-427.

5. Narayanapillai SC, Lin SH, Leitzman P, Upadhyaya P, Baglole CJ, Xing C. Dihydromethysticin (DHM) Blocks Tobacco Carcinogen 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)-Induced O6-Methylguanine in a Manner Independent of the Aryl Hydrocarbon Receptor (AhR) Pathway in C57BL/6 Female Mice. Chemical research in toxicology. 2016;29:1828-1834.

6. Hu Q, Corral P, Narayanapillai SC, Leitzman P, Upadhyaya P, O'Sullivan MG, Hecht SS, Lu J, Xing C. Oral dosing of dihydromethysticin ahead of tobacco carcinogen NNK effectively prevents lung tumorigenesis in A/J mice. Chemical research in toxicology. 2020.

7. Puppala M, Narayanapillai SC, Leitzman P, Sun H, Upadhyaya P, O'Sullivan MG, Hecht SS, Xing C. Pilot in Vivo Structure-Activity Relationship of Dihydromethysticin in Blocking 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone-Induced O(6)-Methylguanine and Lung Tumor in A/J Mice. Journal of medicinal chemistry. 2017;60:7935-7940.

8. Steiner GG. The correlation between cancer incidence and kava consumption. Hawaii Med J. 2000;59:420-422.

9. Foliaki S, Best D, Akau'ola S, Cheng S, Borman B, Pearce N. Cancer incidence in four pacific countries: Tonga, Fiji Islands, Cook Islands and Niue. Pacific health dialog. 2011;17:21-32.

10. Henderson BE, Kolonel LN, Dworsky R, Kerford D, Mori E, Singh K, Thevenot H. Cancer incidence in the islands of the Pacific. Natl Cancer Inst Monogr. 1985;69:73-81.

11. Narayanapillai SC, Leitzman P, O'Sullivan MG, Xing C. Flavokawains a and B in kava, not dihydromethysticin, potentiate acetaminophen-induced hepatotoxicity in C57BL/6 mice. Chemical research in toxicology. 2014;27:1871-1876.

12. Bian T, Corral P, Wang Y, Botello J, Kingston R, Daniels T, Salloum RG, Johnston E, Huo Z, Lu J, Liu AC, Xing C. Kava as a Clinical Nutrient: Promises and Challenges. Nutrients. 2020;12.

13. Hope BT, Nagarkar D, Leonard S, Wise RA. Long-term upregulation of protein kinase A and adenylate cyclase levels in human smokers. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2007;27:1964-1972.

14. Wang YE, S.; Stacy, H.; Narayanapillai, S.; Sharma, A.; Fujioka, N.; Haddad, L.; McLaughlin, J.; Avery, B. A.; Xing, C. A stable isotope dilution tandem mass spectrometry method of major kavalactones and its applications. PloS one. 2018;13:e0197940.

15. Teschke R. Kava hepatotoxicity--a clinical review. Annals of hepatology. 2010;9:251-265.

16. Oncken C, Gonzales D, Nides M, Rennard S, Watsky E, Billing CB, Anziano R, Reeves K. Efficacy and safety of the novel selective nicotinic acetylcholine receptor partial agonist, varenicline, for smoking cessation. Arch Intern Med. 2006;166:1571-1577.

17. Nides M, Oncken C, Gonzales D, Rennard S, Watsky EJ, Anziano R, Reeves KR. Smoking cessation with varenicline, a selective alpha4beta2 nicotinic receptor partial agonist: results from a 7-week, randomized, placebo- and bupropion-controlled trial with 1-year follow-up. Arch Intern Med. 2006;166:1561-1568.

18. Thompson TP, Greaves CJ, Ayres R, Aveyard P, Warren FC, Byng R, Taylor RS, Campbell JL, Ussher M, Michie S, West R, Taylor AH. Factors associated with study attrition in a pilot randomised controlled trial to explore the role of exercise-assisted reduction to stop (EARS) smoking in disadvantaged groups. Trials. 2016;17:524.

16. APPENDIX A: PROPOSED MEASURES FOR TOBACCO USE, CRAVING, ADDICTION, STRESS, AND INSOMNIA

Self-Reported Measures of Smoking Cigarettes

✓ Instructions for Filling Out the Timeline Cigarette Use Calendar

To help us evaluate your cigarette use, we need to get an idea of what your smoking was like in the past_____ days. To do this, we would like you to fill out the attached calendar. Filling out the calendar is not hard! Try to be as accurate as possible.

We recognize you won't have perfect recall. That's **OKAY**.

WHAT TO FILL IN

The idea is to record how many cigarettes you smoked for each day on the calendar. On days when you did not smoke cigarettes, not even one, you should write a "0." It's important that something is written for every day, even if it is a 0".

YOUR BEST ESTIMATE

We realize it isn't easy to recall things with 100% accuracy. If you are not sure whether you smoked 15 or 16 cigarettes or whether you smoked on a Thursday or a Friday, give it your best guess! What is important is that 15 or 16 cigarettes is very different from 1 cigarette. The goal is to get a sense of how frequently you smoked, how much you smoked, and your patterns of smoking.

HELPFUL HINTS

- If you have an appointment book, you can use it to help you recall your use.
- Holidays such as Thanksgiving and Christmas are marked on the calendar to help you recall your smoking. Also, think about how much you smoked on personal holidays & events such as birthdays, vacations, or parties.
- If you have regular patterns to your smoking, you can use these to help you recall your use. For example, some people may only smoke during social situations.

COMPLETING THE CALENDAR

A blank calendar is attached. Write in the number of cigarettes you smoked on each day. The time period we are talking about on the calendar is from_____ to _____. In estimating the number of cigarettes you smoked, be as accurate as possible.

DOUBLE CHECK THAT ALL DAYS ARE FILLED IN BEFORE RETURNING THE CALENDAR.

Before you start look at the **SAMPLE CALENDAR**.

Fagerstrom Test for Nicotine Dependence

1. How soon after you wake up do/did you smoke your first cigarette?

   1[ ]Within 5 minutes [3 points]

   2 [ ]6-30 minutes [2 points]

   3 [ ]31-60 minutes [1 point]

   4 [ ]After 60 minutes [0 points]

2. Do/Did you find it difficult to refrain from smoking in places where it is forbidden, e.g.,in church, at the library, in a cinema, etc.?

   1[ ]Yes [point]

   2[ ]No [0 points]

3. Which cigarette would you hate most to give up?

   1[ ]The first one in the morning [1 point]

   2[ ] All others [0 points]

4. How many cigarettes per day do/did you smoke?

   1[ ]10 or less [0 points]

   2[ ]11-20 [1 point]

   3[ ]21-30 [2 points]

   4[ ]31 or more [3 points]

5. Do/did you smoke more frequently during the first hours after waking than during therest of the day?

   1 [ ]Yes [1 point]

   2[ ]No [0 points]

6. Do/did you smoke if you are so ill that you are in bed most of the day?1[ ]Yes [1 point]

   2[ ]No [0 points]

Modified Cigarette Evaluation Questionnaire

If you have smoked since you last completed this questionnaire, please mark the number that best represents how smoking made you feel (1—not at all, 2—very little, 3—a little, 4—moderately, 5—a lot, 6—quite a lot, 7—extremely).

1. Was smoking satisfying?
2. Did cigarettes taste good?
3. Did you enjoy the sensations in your throat and chest?
4. Did smoking calm you down?
5. Did smoking make you feel more awake?
6. Did smoking make you feel less irritable?
7. Did smoking help you concentrate?
8. Did smoking reduce your hunger for food?
9. Did smoking make you dizzy?
10. Did smoking make you nauseous?
11. Did smoking immediately relieve your craving for a cigarette?
12. Did you enjoy smoking?

Brief Questionnaire on Smoking Urges

*Indicate how much you agree or disagree with each of the following statements by placing a single checkmark (like this: [✔]) by a number ranging from 1 (strongly disagree) to 7 (strongly agree). The closer you place your checkmark to one end or the other indicates the strength of your disagreement or agreement. Please complete every item. We are interested in how you are thinking or feeling**right now** as you are filling out this questionnaire.*

1. I have a desire for a cigarette right now.

1 [ ] STRONGLY DISAGREE 2 [ ] 3 [ ] 4 [ ] 5 [ ] 6 [ ] 7 [ ] STRONGLY AGREE

2. Nothing would be better than smoking a cigarette right now.

1 [ ] STRONGLY DISAGREE 2 [ ] 3 [ ] 4 [ ] 5 [ ] 6 [ ] 7 [ ] STRONGLY AGREE

3. If it were possible, I probably would smoke right now.

1 [ ] STRONGLY DISAGREE 2 [ ] 3 [ ] 4 [ ] 5 [ ] 6 [ ] 7 [ ] STRONGLY AGREE

4. I could control things better right now if I could smoke.

1 [ ] STRONGLY DISAGREE 2 [ ] 3 [ ] 4 [ ] 5 [ ] 6 [ ] 7 [ ] STRONGLY AGREE

5. All I want right now is a cigarette.

1 [ ] STRONGLY 2 [ ] 3 [ ] 4 [ ] 5 [ ] 6 [ ] 7 [ ] STRONGLY

DISAGREE]]]]] AGREE

6. I have an urge for a cigarette.

1 [ ] STRONGLY DISAGREE 2 [ ] 3 [ ] 4 [ ] 5 [ ] 6 [ ] 7 [ ] STRONGLY AGREE

7. A cigarette would taste good now.

1 [ ] STRONGLY DISAGREE 2 [ ] 3 [ ] 4 [ ] 5 [ ] 6 [ ] 7 [ ] STRONGLY AGREE

8. I would do almost anything for a cigarette now.

1 [ ] STRONGLY DISAGREE 2 [ ] 3 [ ] 4 [ ] 5 [ ] 6 [ ] 7 [ ] STRONGLY AGREE

9. Smoking would make me less depressed.

1 [ ] STRONGLY DISAGREE 2 [ ] 3 [ ] 4 [ ] 5 [ ] 6 [ ] 7 [ ] STRONGLY AGREE

10. I am going to smoke as soon as possible.

1 [ ] STRONGLY DISAGREE 2 [ ] 3 [ ] 4 [ ] 5 [ ] 6 [ ] 7 [ ] STRONGLY AGREE

Perceived Stress Scale

For each question choose from the following alternatives:
0 - never 1 - almost never 2 - sometimes 3 - fairly often 4 - very often

_____ l. In the last month, how often have you been upset because of something that happened unexpectedly?

_____ 2. In the last month, how often have you felt that you were unable to control theimportant things in your life?

_____ 3. In the last month, how often have you felt nervous and stressed?

_____ 4. In the last month, how often have you felt confident about your ability to handle your personal problems?

_____ 5. In the last month, how often have you felt that things were going your way?

_____ 6. In the last month, how often have you found that you could not cope withall the things that you had to do?

_____ 7. In the last month, how often have you been able to control irritations inyour life?

_____ 8. In the last month, how often have you felt that you were on top of things?

_____ 9. In the last month, how often have you been angered because of things thathappened that were outside of your control?

_____ 10. In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?

Insomnia Severity Scale

Insomnia Severity Index

The Insomnia Severity Index has seven questions. The seven answers are added up to get a total score. When you haveyour total score, look at the 'Guidelines for Scoring/Interpretation' below to see where your sleep difficulty fits.

For each question, please CIRCLE the number that best describes your answer.

Please rate the CURRENT (i.e. LAST 2 WEEKS) SEVERITY of your insomnia problem(s).

Insomnia Problem	None	Mild	Moderate	Severe	Very Severe
1. Difficulty falling asleep	0	1	2	3	4
2. Difficulty staying asleep	0	1	2	3	4
3. Problems waking up too early	0	1	2	3	4

4. How SATISFIED/DISSATISFIED are you with your CURRENT sleep pattern?

Very Satisfied	Satisfied	Moderately Satisfied	Dissatisfied	Very Dissatisfied
0	1	2	3	4

5. How NOTICEABLE to others do you think your sleep problem is in terms of impairing the quality of your life?Not at all

Noticeable	A Little	Somewhat	Much	Very Much Noticeable
0	1	2	3	4

6. How WORRIED/DISTRESSED are you about your current sleep problem?Not at all

Worried	A Little	Somewhat	Much	Very Much Worried
0	1	2	3	4

7. To what extent do you consider your sleep problem to INTERFERE with your daily functioning (e.g. daytimefatigue, mood, ability to function at work/daily chores, concentration, memory, mood, etc.) CURRENTLY?

Not at all Interfering	A Little	Somewhat	Much	Very Much Interfering
0	1	2	3	4

Guidelines for Scoring/Interpretation:

Add the scores for all seven items (questions 1 + 2 + 3 + 4 + 5 +6 + 7) =_____

your total scoreTotal score categories:

0–7 = No clinically significant insomnia

8–14 = Subthreshold insomnia

15–21 = Clinical insomnia (moderate severity)22–28 = Clinical insomnia (severe)

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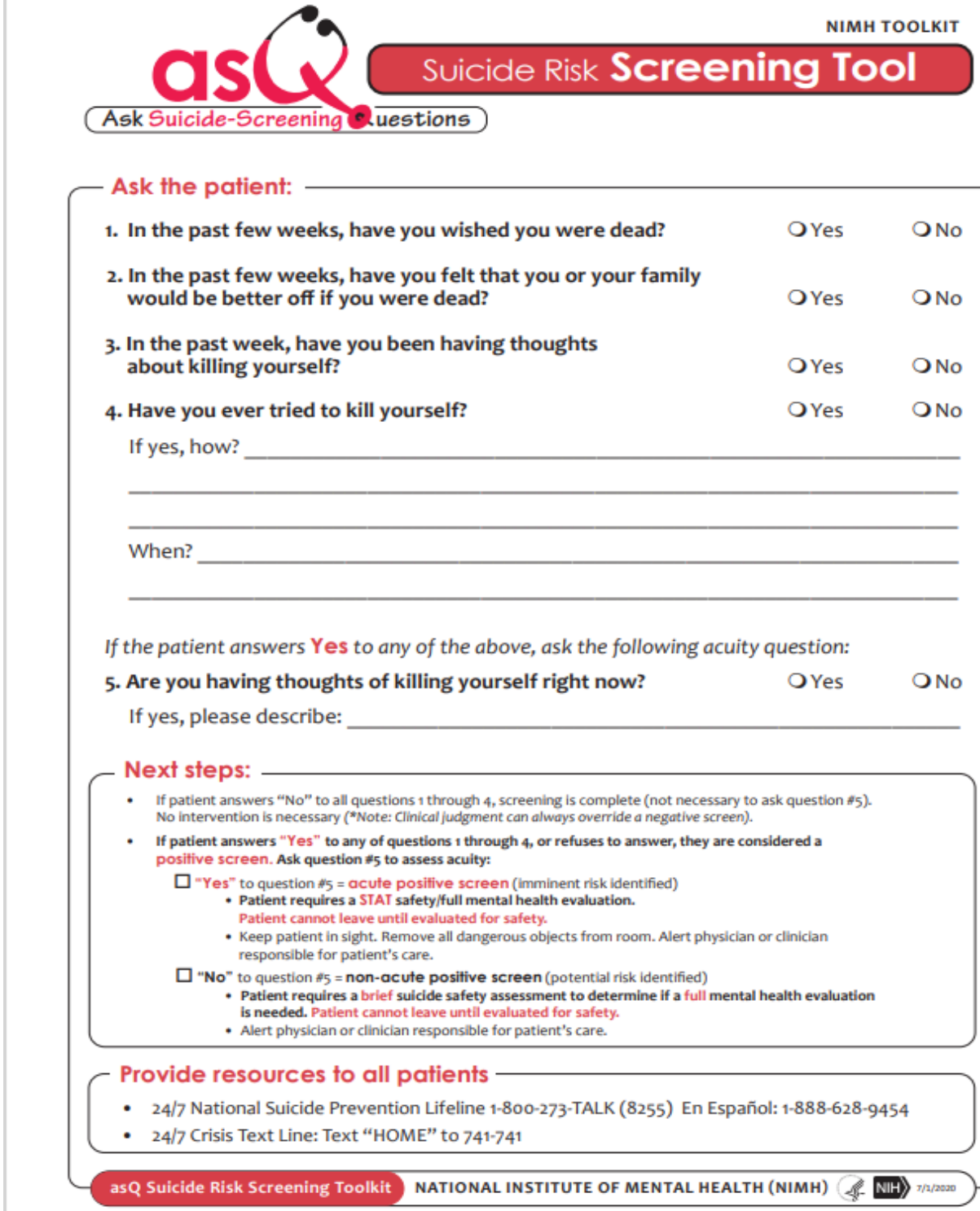
Ask Suicide-Screening Questions (ASQ)



NIMH TOOLKIT

asQ Suicide Risk Screening Tool

Ask Suicide-Screening Questions

Ask the patient:

1. **In the past few weeks, have you wished you were dead?** ❍ Yes ❍ No
2. **In the past few weeks, have you felt that you or your family would be better off if you were dead?** ❍ Yes ❍ No
3. **In the past week, have you been having thoughts about killing yourself?** ❍ Yes ❍ No
4. **Have you ever tried to kill yourself?** ❍ Yes ❍ No

   If yes, how? _____

   _____

   _____

   When? _____

   _____

*If the patient answers **Yes** to any of the above, ask the following acuity question:*

5. **Are you having thoughts of killing yourself right now?** ❍ Yes ❍ No

   If yes, please describe: _____

Next steps:

- If patient answers "No" to all questions 1 through 4, screening is complete (not necessary to ask question #5). No intervention is necessary *(*Note: Clinical judgment can always override a negative screen).*
- **If patient answers "Yes" to any of questions 1 through 4, or refuses to answer, they are considered a positive screen. Ask question #5 to assess acuity:**
  - ☐ **"Yes"** to question #5 = **acute positive screen** (imminent risk identified)
    - **Patient requires a STAT safety/full mental health evaluation.** Patient cannot leave until evaluated for safety.
    - Keep patient in sight. Remove all dangerous objects from room. Alert physician or clinician responsible for patient's care.
  - ☐ **"No"** to question #5 = **non-acute positive screen** (potential risk identified)
    - **Patient requires a brief suicide safety assessment to determine if a full mental health evaluation is needed.** Patient cannot leave until evaluated for safety.
    - Alert physician or clinician responsible for patient's care.

Provide resources to all patients

- 24/7 National Suicide Prevention Lifeline 1-800-273-TALK (8255) En Español: 1-888-628-9454
- 24/7 Crisis Text Line: Text "HOME" to 741-741

asQ Suicide Risk Screening Toolkit | NATIONAL INSTITUTE OF MENTAL HEALTH (NIMH) | NIH | 7/1/2020

PATH
Population Assessment of Tobacco and Health
A collaboration between the NIH and FDA

PATH Nicotine Exposure Questionnaire

Have you used any of the following products today, yesterday, or the day before yesterday?
(If you don't know an answer or don't want to provide one, you may leave the question blank.)

1 Cigarettes	YES ☐ / NO ☐	When did you last smoke a cigarette? ☐ In the past hour ☐ Sometime today, but more than an hour ago ☐ Yesterday ☐ Day before yesterday	What time of day did you last smoke a cigarette? ☐ Between midnight and 6AM ☐ After 6AM but before noon ☐ Between noon and 6PM ☐ After 6PM but before midnight	During the day you last smoked a cigarette, how many cigarettes did you smoke? ☐☐☐
2 Electronic nicotine products that contain nicotine (such as e-cigarettes, e-hookahs, e-cigars, or e-pipes)	YES ☐ / NO ☐	When did you last use an e-product? ☐ In the past hour ☐ Sometime today, but more than an hour ago ☐ Yesterday ☐ Day before yesterday	What time of day did you last use an e-product? ☐ Between midnight and 6AM ☐ After 6AM but before noon ☐ Between noon and 6PM ☐ After 6PM but before midnight	During the day you last used an e-product, how many puffs did you take? ☐☐☐
3 Traditional cigars filled with tobacco	YES ☐ / NO ☐	When did you last smoke a traditional cigar? ☐ In the past hour ☐ Sometime today, but more than an hour ago ☐ Yesterday ☐ Day before yesterday	What time of day did you last smoke a traditional cigar? ☐ Between midnight and 6AM ☐ After 6AM but before noon ☐ Between noon and 6PM ☐ After 6PM but before midnight	During the day you last smoked a traditional cigar, how many did you smoke? ☐☐☐
4 Cigarillos filled with tobacco	YES ☐ / NO ☐	When did you last smoke a cigarillo? ☐ In the past hour ☐ Sometime today, but more than an hour ago ☐ Yesterday ☐ Day before yesterday	What time of day did you last smoke a cigarillo? ☐ Between midnight and 6AM ☐ After 6AM but before noon ☐ Between noon and 6PM ☐ After 6PM but before midnight	During the day you last smoked a cigarillo, how many did you smoke? ☐☐☐
5 Filtered cigars filled with tobacco	YES ☐ / NO ☐	When did you last smoke a filtered cigar? ☐ In the past hour ☐ Sometime today, but more than an hour ago ☐ Yesterday ☐ Day before yesterday	What time of day did you last smoke a filtered cigar? ☐ Between midnight and 6AM ☐ After 6AM but before noon ☐ Between noon and 6PM ☐ After 6PM but before midnight	During the day you last smoked a filtered cigar, how many did you smoke? ☐☐☐
6 Pipe filled with tobacco	YES ☐ / NO ☐	When did you last smoke a pipe filled with tobacco? ☐ In the past hour ☐ Sometime today, but more than an hour ago ☐ Yesterday ☐ Day before yesterday	What time of day did you last smoke a pipe filled with tobacco? ☐ Between midnight and 6AM ☐ After 6AM but before noon ☐ Between noon and 6PM ☐ After 6PM but before midnight	During the day you last smoked a pipe, how many bowls filled with tobacco did you smoke? ☐☐☐

PATH Nicotine Exposure Questionnaire

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PATH Nicotine Exposure Questionnaire

Have you used any of the following products today, yesterday, or the day before yesterday?
(If you don't know an answer or don't want to provide one, you may leave the question blank.)

7 Hookah filled with tobacco

YES ☐ NO ☐

When did you last smoke tobacco in a hookah?
- ☐ In the past hour
- ☐ Sometime today, but more than an hour ago
- ☐ Yesterday
- ☐ Day before yesterday

What time of day did you last smoke tobacco in a hookah?
- ☐ Between midnight and 6AM
- ☐ After 6AM but before noon
- ☐ Between noon and 6PM
- ☐ After 6PM but before midnight

During the day you last smoked hookah, how many puffs did you take? ☐☐☐

8 Snus

YES ☐ NO ☐

When did you last use snus?
- ☐ In the past hour
- ☐ Sometime today, but more than an hour ago
- ☐ Yesterday
- ☐ Day before yesterday

What time of day did you last use snus?
- ☐ Between midnight and 6AM
- ☐ After 6AM but before noon
- ☐ Between noon and 6PM
- ☐ After 6PM but before midnight

During the day you last used snus, how many times did you use it? ☐☐☐

9 Smokeless tobacco
(such as moist snuff, dip, spit, or chew)

YES ☐ NO ☐

When did you last use smokeless tobacco?
- ☐ In the past hour
- ☐ Sometime today, but more than an hour ago
- ☐ Yesterday
- ☐ Day before yesterday

What time of day did you last use smokeless tobacco?
- ☐ Between midnight and 6AM
- ☐ After 6AM but before noon
- ☐ Between noon and 6PM
- ☐ After 6PM but before midnight

During the day you last used smokeless tobacco, how many times did you use it? ☐☐☐

10 IQOS

YES ☐ NO ☐

When did you last use IQOS?
- ☐ In the past hour
- ☐ Sometime today, but more than an hour ago
- ☐ Yesterday
- ☐ Day before yesterday

What time of day did you last use IQOS?
- ☐ Between midnight and 6AM
- ☐ After 6AM but before noon
- ☐ Between noon and 6PM
- ☐ After 6PM but before midnight

During the day you last used IQOS, how many HeatSticks did you use? ☐☐☐

11 Nicotine pouches
(such as Zyn, on!, or Velo)

YES ☐ NO ☐

When did you last use a nicotine pouch?
- ☐ In the past hour
- ☐ Sometime today, but more than an hour ago
- ☐ Yesterday
- ☐ Day before yesterday

What time of day did you last use a nicotine pouch?
- ☐ Between midnight and 6AM
- ☐ After 6AM but before noon
- ☐ Between noon and 6PM
- ☐ After 6PM but before midnight

During the day you last used a nicotine pouch, how many did you use? ☐☐☐

12 Other types of oral nicotine products
(such as Velo lozenges, Rogue tablets, Lucy gum, or Pixotine toothpicks)

YES ☐ NO ☐

When did you last use an oral nicotine product?
- ☐ In the past hour
- ☐ Sometime today, but more than an hour ago
- ☐ Yesterday
- ☐ Day before yesterday

What time of day did you last use an oral nicotine product?
- ☐ Between midnight and 6AM
- ☐ After 6AM but before noon
- ☐ Between noon and 6PM
- ☐ After 6PM but before midnight

During the day you last used an oral nicotine product, which types did you use? Choose all that apply.
- ☐ Velo nicotine lozenges
- ☐ Rogue nicotine lozenges
- ☐ Verve nicotine discs
- ☐ Rogue nicotine tablets
- ☐ Lucy nicotine gum
- ☐ Pixotine nicotine toothpicks
- ☐ Stonewall dissolvable tobacco
- ☐ Something else (SPECIFY): _____

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PATH Nicotine Exposure Questionnaire

Have you used any of the following products today, yesterday, or the day before yesterday?
(If you don't know an answer or don't want to provide one, you may leave the question blank.)

13 Nicotine patch

YES ☐ NO ☐

When you last used a nicotine patch, when did you remove it?
- ☐ I am currently wearing a nicotine patch
- ☐ In the past hour
- ☐ Sometime today, but more than an hour ago
- ☐ Yesterday
- ☐ Day before yesterday

How many hours has it been since you removed a nicotine patch?
- ☐ I am currently wearing a nicotine patch
- ☐ 1 to 4 hours
- ☐ 5 to 11 hours
- ☐ More than 12 hours

When you last used a nicotine patch, what strength did you use? (If you are currently wearing a nicotine patch, please answer for the patch you are currently wearing.)
- ☐ 21 mg (Step 1)
- ☐ 14 mg (Step 2)
- ☐ 7 mg (Step 3)
- ☐ Some other strength (SPECIFY): _____
- ☐ I don't know

14 Nicotine gum, a nicotine inhaler, nicotine nasal spray or lozenge

YES ☐ NO ☐

When did you last use nicotine gum, a nicotine inhaler, nicotine nasal spray or lozenge?
- ☐ In the past hour
- ☐ Sometime today, but more than an hour ago
- ☐ Yesterday
- ☐ Day before yesterday

What time of day did you last use nicotine gum, a nicotine inhaler, nicotine nasal spray or lozenge?
- ☐ Between midnight and 6AM
- ☐ After 6AM but before noon
- ☐ Between noon and 6PM
- ☐ After 6PM but before midnight

During the day you last used nicotine gum, a nicotine inhaler, nicotine nasal spray or lozenge, how many did you use? ☐☐☐

15 Chantix, varenicline, Wellbutrin, Zyban, or bupropion

YES ☐ NO ☐

When did you last use Chantix, varenicline, Wellbutrin, Zyban, or bupropion?
- ☐ In the past hour
- ☐ Sometime today, but more than an hour ago
- ☐ Yesterday
- ☐ Day before yesterday

What time of day did you last use Chantix, varenicline, Wellbutrin, Zyban, or bupropion?
- ☐ Between midnight and 6AM
- ☐ After 6AM but before noon
- ☐ Between noon and 6PM
- ☐ After 6PM but before midnight

During the day you last used Chantix, varenicline, Wellbutrin, Zyban, or bupropion, how many did you take? ☐☐☐

16 Marijuana that is vaped in an e-cigarette, vape pen, or electronic nicotine product

YES ☐ NO ☐

When did you last use marijuana in an e-product?
- ☐ In the past hour
- ☐ Sometime today, but more than an hour ago
- ☐ Yesterday
- ☐ Day before yesterday

What time of day did you last use marijuana in an e-product?
- ☐ Between midnight and 6AM
- ☐ After 6AM but before noon
- ☐ Between noon and 6PM
- ☐ After 6PM but before midnight

17 Marijuana that is smoked in a blunt cigar, cigarillo, or filtered cigar

YES ☐ NO ☐

When did you last smoke marijuana in a blunt?
- ☐ In the past hour
- ☐ Sometime today, but more than an hour ago
- ☐ Yesterday
- ☐ Day before yesterday

What time of day did you last smoke marijuana in a blunt?
- ☐ Between midnight and 6AM
- ☐ After 6AM but before noon
- ☐ Between noon and 6PM
- ☐ After 6PM but before midnight

18 Marijuana that is smoked in a joint, pipe, hookah, or bong

YES ☐ NO ☐

When did you last smoke marijuana in a joint, pipe, hookah, or bong?
- ☐ In the past hour
- ☐ Sometime today, but more than an hour ago
- ☐ Yesterday
- ☐ Day before yesterday

What time of day did you last smoke marijuana in a joint, pipe, hookah, or bong?
- ☐ Between midnight and 6AM
- ☐ After 6AM but before noon
- ☐ Between noon and 6PM
- ☐ After 6PM but before midnight

Date: ☐☐/☐☐/2 0☐☐ (m m / d d / y y y y)

Participant ID: _____

17. APPENDIX B. SCHEDULE OF EVENTS

Visit: Procedure:	SCREENING[2] (≤ 21 days prior to Day 1)	BASELINE (Day 1)	WEEK 1 (Day 8 +/- 3 days)	WEEK 2 (Day 15 +/- 3 days)	WEEK 4 (Day 29 +/- 3 days)	WEEK 8 FOLLOW UP (DAY 57 +/- 3 days)	WEEK 12 FOLLOW UP (DAY 85 +/- 7 days)
Informed Consent	X						
Demographic Information	X						
Relevant Medical History and Concomitant Medication Review[3,4]	X						
Brief Physical Exam	X				X		
CO breath test	X	X	X	X	X	X	X
Height	X						
Weight	X						
Biomarker Assessment-(blood and urine)		X	X	X	X	X	X
Labs (CMP)	X	X	X	X	X	X	X
Pregnancy Test (Urine)	X						
Randomization	X						
Administration of Study Drug		X	X	X			
Review and/or dispense subject Diary		X	X	X	X		
Adverse Event Review		X	X	X	X	X	X
24-h urine- supplies	X	X	X	X	X	X	
Questionnaires	X[1]	X	X	X	X	X	X

Insert information, as appropriate, if superscripts are used within the table. Examples provided below.

Abbreviation(s): CMP=12 item complete metabolic profile (sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose, alkaline phosphatase, AST, ALT, total bilirubin)

1. ASQ questionnaire only, given at screening
2. Screening procedures performed per Standard of Care within the screening window can be used even if prior to consent.
3. Only to be reviewed at time of screening. Concomitant medications are defined as all medications participant is actively taking at time of enrollment.
4. Relevant medical history is defined as any diagnosis of depression or cancer