Cardiovascular, Immune and Psychosocial Benefits of Reduced Cocaine Use
NCT03224546
January 9, 2024

1. BACKGROUND

Promoting reductions in problem behaviors is common in medical practice wherein at-risk individuals are counseled to make moderate, sustainable changes in lifestyle (e.g., reduced high fat food intake in individuals at risk for myocardial infarction). Reducing the percentage of heavy drinking days in individuals with alcohol use disorder is an accepted intervention target in alcohol addiction treatment, yet for other drug use disorders, *complete abstinence* remains the standard for demonstrating treatment efficacy. Interventions that promote *reductions* in drug use should improve health, biochemical and psychosocial outcomes. Little prospective research has been conducted to demonstrate the benefits of reduced drug use, however. Demonstrating the benefits of reduced cocaine (COC) use would represent a significant advance in treatment development by changing expectations for outcomes from possible interventions. Adopting this outcome would accelerate identification of promising treatments and advance research and practice in the field.

COC use produces a number of health detriments that could be ameliorated by COC use reduction. For example, COC increases heart rate, blood pressure and vasoconstriction, with chronic use producing changes in vasculature that increase the likelihood of myocardial infarction, atherosclerosis and stroke. These changes are likely mediated through dysregulated endothelial and platelet activity produced by COC, which results in physiological sequelae including increased vasospasm and hypertension. COC use also disrupts immune function, resulting in a pro-inflammatory state and abnormal cell-mediated immunity. This cascade can increase vulnerability to contracting infections or exacerbate existing infections. Individuals with COC use disorder (CUD) also experience a range of psychosocial problems including increased likelihood of co-morbid mental health diagnoses, inhibitory control deficits, risky sexual and drug use behavior and unemployment. Complete COC abstinence improves these potentially devastating consequences of COC use. Some research indicates that reduced COC use also benefits these domains, but this effect has not been *prospectively or comprehensively* demonstrated, preventing adoption of reduced use as an efficacy indicator in clinical trials.

To fill this critical knowledge gap, we propose a randomized, controlled 12-week trial using incentives to reduce COC use, with an additional 24 weeks of follow up. Over 5 years, subjects will be randomly assigned to one of three groups (n=66 completers/group): 1) high value incentives for COC abstinence in which frequency of COC use is expected to be substantially reduced or eliminated, 2) low value incentives for COC abstinence in which frequency of COC use is expected to be reduced or 3) a non-contingent control group, in which frequency of COC use is expected to remain stable. Three specific aims are proposed:

First, this study seeks to demonstrate that reduced COC use improves physiological and biochemical indicators (i.e., biomarkers) of cardiovascular function. Improvements in cardiovascular function will be assessed with physiological measures of cardiovascular fitness (e.g., peripheral arterial tonomotry) and biomarkers of endothelial (e.g., endothelin-1) and platelet (e.g., soluble CD40L) function.

Second, this study seeks to demonstrate that reduced COC use improves physiological indicators and biomarkers of immune function. Improvements will be assessed with a physiological measure (i.e., delayed-type hypersensitivity) and biomarkers of immune function (e.g., tumor necrosis factor-α, microbiome indicators).

Third, this study seeks to demonstrate that reduced COC use improves psychosocial function. Psychosocial improvements will be assessed with standardized observer and self-reported measures of mental health, drug use and risky behavior, as well as validated and sensitive cognitive behavioral tasks.

Our overarching hypothesis is that individuals assigned to the active treatment conditions (i.e., those who reduce their COC use) will display health improvements compared to individuals assigned to the non-contingent control group both during and after treatment. A “dose-response” is expected whereby individuals assigned to the high value condition will display greater reductions in COC use, and consequently greater improvements, relative to the low value group. We further hypothesize that 1) individuals assigned to active treatment conditions will display improvements from baseline through treatment completion and into follow up and 2) biomarker improvements will predict physiological outcomes.

This research will fill a critical knowledge gap with impactful information about the physiological, biochemical and psychosocial benefits of reduced COC use. Innovations of this research will advance the field by: 1) using multifaceted health outcomes to provide prospective evidence supporting reduced drug use as a viable endpoint for COC treatment development, 2) identifying biochemical indicators of health improvements

associated with reduced COC use and 3) laying the foundation for a paradigm-shifting definition of COC treatment success, thereby challenging expectations for outcomes in behavioral and pharmacological intervention development. These innovations will accelerate identification of promising treatments for CUD, resulting in a sustained and powerful impact on scientific and clinical practice.

2. OBJECTIVES

The primary objective of this study is to demonstrate that reduced cocaine use results in improved cardiovascular, immune and psychosocial outcomes.

3. STUDY DESIGN

Randomized, controlled, single-blind 12-week outpatient trial using incentives to promote reduced cocaine use.

4. STUDY POPULATION

Up to 500 individuals will be screened to participate in this protocol. We intend to enroll 300 (150 men, 150 women) subjects, with 198 completers. These individuals must be English-speaking, English-reading subjects 18 years and older of diverse racial and ethnic background. Enrollment in this protocol will occur between September 1, 2017 and August 31, 2022. Subjects will be required to provide legal proof of age.

Inclusion Criteria:

-Age 18 to 65

-Self-report of recent cocaine use verified by a cocaine-positive urine sample

-Meet moderate-severe Cocaine Use Disorder Criteria

-Seeking treatment for their cocaine use

-Able to commit to 12-week intervention, plus 24-week follow up

-Participants who have taken antibiotics within 30 days of sample collection will be excluded from the microbiome assay.

Exclusion Criteria:

-History of serious physical or psychiatric disease (e.g., physical dependence on any drug requiring medically managed detoxification, unstable angina, uncontrolled cardiac arrhythmia, aortic stenosis, self-reported compromised immune function, extreme hypersensitivity/allergy to candida yeast or similar products, severe diagnosis for other substance use disorder) that would interfere with study participation

-Current physical or psychiatric disease that would interfere with study participation

-Poor venous access, precluding blood draws

During the initial screening interview and prior to sessions, potential subjects will be asked to provide a urine specimen that will be screened for the presence of a range of drugs including amphetamine, benzodiazepines, barbiturates, cocaine, tetrahydrocannabinol (THC) and opioids. Temperature will be recorded and the presence of adulterants will be tested using measures of creatinine, nitrite, pH, bleach, and specific gravity. Temperature and adulterant tests are included in the CLIAwaived brand rapid drug test cup. Evidence of urine sample adulteration will result in subject dismissal from the study.

5. SUBJECT RECRUITMENT METHODS AND PRIVACY

Study subjects will be recruited using UK PR and IRB approved advertisements under our existing screening protocol (#03-0509). Advertisements will be posted in the local community via newspaper ads, physical community bulletin boards, online community bulletin boards (e.g., Craigslist, Lexington Herald-Leader online). Advertisements posted online will conform to terms of use for each specific bulletin board. We will also recruit subjects through word-of-mouth. Subjects will make initial contact by phone with one of our recruiters who have completed the research training and HIPAA compliance web-based teaching models. If the subject self-discloses information that would make him/her potentially eligible for the study, they will be invited to come in for a screening appointment. Screening is completed by one of our research assistants at the UK

Laboratory of Human Behavioral Pharmacology (LHBP). Study investigators may interact with subjects in this setting and appropriate cautions are in place to ensure privacy during the intake process.

6. INFORMED CONSENT PROCESS

All potential subjects that are identified using the subject recruitment methods noted above will provide informed consent prior to participating in the protocol. Subjects that meet the eligibility criteria noted above will come to the LHBP and will undergo a field sobriety test and provide an expired air sample that will be tested for the presence of alcohol. If the subject passes the field sobriety test (walk and turn, one-leg balance [timed], finger-to-nose and backwards-counting tasks) and the expired air sample is negative, he or she will then be given a copy of the approved informed consent document to read and sign. After reading the consent document, the PI on this protocol or his designee will address any questions the subject may have in order to assess the subject's understanding of the protocol. After this, the subject will receive a copy of the informed consent document and will sign a form indicating that they have received a copy of the form they read and signed.

7. RESEARCH PROCEDURES

Subjects who are deemed potentially eligible after an initial telephone screen and express interest in participation will be scheduled for an in-person, intake interview. After providing informed consent, subjects will self-report medical, psychiatric, drug use and substance use disorder treatment histories. They will also be asked for contact information for themselves (e.g., postal address, phone, text message, email, social media) and two other individuals who know how to reach the subject. This information will be collected as a way to minimize loss of contact with subjects and prevent missing data. To further prevent missing data, subjects will be offered transportation to/from the laboratory for study visits. We are using similar methods in our ongoing clinical trial, as noted above, resulting in very little missing data.

Preliminary health assessments will include vital signs, weight and height measurement, urine drug screening, standard laboratory chemistries (i.e., hemogram with differential, c reactive protein, chemistry panel 23, lipid panel, troponin, uric acid, cortisol) and an electrocardiogram (ECG). Psychological assessments will include a DSM-5 diagnostic interview (SCID-5) and the Addiction Severity Index-Lite (ASI), conducted by trained and qualified interviewers. The ASI will complement the SCID-5 by providing data on physical and mental health, alcohol and drug use, employment, legal status and family/social support. Study investigators will review these materials for inclusion/exclusion criteria and if a subject is deemed eligible and accepts the offer to participate, he/she will complete additional baseline measures (e.g., peripheral arterial tonometry) and be urn-randomized to one of three study groups. Any abnormalities detected at screening that result in exclusion from participation will be disclosed to subjects, who will be encouraged to follow up with their physician or the public health department. Should abnormalities be detected after randomization into the study, our study physician, Dr. Hays, will determine the best course of action. Dr. Hays will consult with Dr. Smyth should abnormalities be related to cardiovascular outcomes.

Random Assignment

After screening, consenting subjects deemed eligible will be enrolled in a 12-week intervention, with a 24-week post intervention follow up period. Subjects will be urn-randomized to one of three groups: 1) high value incentives, 2) low value incentives or 3) non-contingent control. An urn randomization process will be used to assign subjects to the three conditions. This method is designed to balance groups on important biological variables that may independently influence outcome. Subjects will be randomized based on sex (male/female), age (>35/≤35 years) and COC use (>15/≤15 days used in the past 30). These characteristics will be determined based on responses to the ASI completed during screening. Dr. Stoops will perform the randomization and notify non-blind study staff of group assignment. Subjects will be assigned 1:1:1 to the high value, low value and non-contingent control groups.

Alternative Reinforcers for Reduced COC Use: Schedules of Reinforcement and Procedures

Subjects will be assigned to one of two schedules of reinforcement (high and low value incentives) for providing BE-negative urine samples or to a non-contingent control group who will receive money for simply providing a urine sample at each visit.

Subjects assigned to the high value condition will receive $55 for providing a BE-negative urine sample. Subjects assigned to the low value condition will receive $13 for providing a BE-negative urine sample. Providing a BE-positive urine sample will result in no payment for that sample in either the high or low value group. Subjects assigned to the control condition will receive $13 per urine sample they provide independent of test results. Subjects will also be paid for attending study visits during the protocol (see below), independent of urine result outcome, to increase attendance and minimize missing data.

The nature of the intervention prevents subjects from being blind to their assigned condition (i.e., subjects need to be told whether they will earn money for BE-negative urine samples or will earn money for simply providing a urine sample), but subjects will be instructed not to discuss the details of their participation with other subjects or study staff. To enhance rigor and reduce bias, study staff who complete post-randomization assessments, as well as the biostatistician, will be blind to the assigned condition for each subject.

Defining Reduction in Frequency of COC Use. Subjects will provide observed urine samples thrice weekly (i.e., Monday, Wednesday and Friday) during the 12-week intervention. This thrice weekly urine collection schedule was selected based on the detection time of BE in urine (i.e., up to 72 hours after use; 89) and because the study on which our incentive schedule is based used thrice weekly testing. All urine samples will be coded as positive or negative using qualitative urine BE screens that have a 300 ng/ml cutoff, a criterion used in many recent clinical trials and the criterion used by Higgins and colleagues (Higgins et al., 2007). Using this approach will allow estimates of the levels of reduction observed in each of the three groups (see above).

The number of BE-negative urine samples provided across each week of the trial, out of a maximum of three each week, will be calculated for each subject to determine how group assignment impacted frequency of use. *Experts recently recommended that frequency of use, rather than quantity of use, be the target for reduction (Kiluk et al., 2016).* Overall percentage and number of BE-negative urine samples across the trial will also be calculated. Subjects are likely to vary in their response to alternative reinforcers, especially between the three conditions, which will provide a range of scores that can be used to predict health outcomes. This variability should also permit exploratory analyses (see below) that will reveal threshold levels of change (e.g., 25%, 50%, 75% negative samples) that are associated with beneficial health outcomes.

Individual Counseling

To provide some benefit to all subjects in addition to health screening and monetary remuneration, all subjects will receive supportive behavioral therapy which provides clinical recommendations for reducing or ceasing COC use. Manual-guided treatment (the Substance Abuse and Mental Health Services Administration's Counselor's Treatment Manual: Matrix Intensive Outpatient Treatment for People with Stimulant Use Disorders) will be conducted weekly with a masters or graduate level psychologist, social worker or counselor, who will remain blind to assigned conditions. Based on our current experience, this counseling will also enhance retention.

Measures

Cardiovascular Health. Cardiovascular health will be measured 12-lead ECGs, PAT using the Endo-PAT2000 system (Itamar Medical, Caesarea, Israel) which measures digital arterial pulse volume at rest and after hyperemia to evaluate coronary endothelial function, resting vital signs (i.e., heart rate and blood pressure) and biomarkers of cardiovascular function, specifically focusing on endothelial and platelet function. The PAT outcome will be the reactive hyperemia index. ECGs will be completed at the CSC and outcomes will include ventricular rate, PR interval, QRS interval and QT/QTc duration. Resting vital signs (i.e., heart rate and blood pressure) will be measured at the LHBP using an automated monitor after a subject has been seated quietly for 5 minutes.

The biomarkers of cardiovascular function will include the endothelial function measures endothelin-1, stromal cell derived factor-1 and soluble intracellular adhesion molecule-1. The platelet function measures will include soluble CD40L and neutrophil activating peptide-2. These specific markers were selected because they

are altered in COC users and improved following COC abstinence. Moreover, these measures can be conducted using ELISA assays, which are more readily available to clinicians and therefore more easily implemented should these markers be adopted for monitoring the health of active COC users. Levels of these markers will be determined with blood samples collected at the time points noted below and analyzed by the UK Biochemical Analysis Laboratory (BAL) using commercially available assays (e.g., R&D Systems Endothelin-1 QuantiGlo ELISA). Blood will be drawn using standard, sterile procedures and will be prepared, stored and analyzed according to commercial assay instructions.

Immune Health. Immune health will be measured using a physiological outcome of cellular mediated immunity, DTH to subcutaneous candida yeast, as well as biomarkers of immune function. To determine DTH, which is positively correlated with in vitro T Cell IL-2 production and survival time in older adults and HIV patients, 0.1 ml of antigen derived from candida yeast (Candin®, Allermed, San Diego, CA) will be injected subcutaneously into subjects' non-dominant forearms. DTH responses will be evaluated 48 hours later by taking the mean of the longest and orthogonal diameters of each induration using the ballpoint pen method, in which a line is drawn with a ballpoint pen toward the margin of the reaction. When resistance due to induration is encountered, the pen is lifted. This method defines the margins of the induration. Because pregnancy can alter immune function biomarkers, we will conduct urine tests for pregnancy monthly.

The biomarkers of immune function will include the anti-inflammatory cytokine IL-10, the pro-inflammatory cytokines TNF-α and IL-6, as well as CRP, a general indicator of inflammation and also a marker of cardiovascular health impacted by COC use. TNF-α, IL-6 and IL-10 are altered in active COC users. The other pro-inflammatory cytokines were selected for testing because they represent various stages of the inflammatory cascade (e.g., TNF-α to IL-6 to CRP). Measuring these pro-inflammatory cytokines along with the anti-inflammatory cytokine IL-10 will reveal immune system improvements produced by reduced COC use. We will also assess Granulate-Colony Stimulating Factor (G-CSF) and Chemokine Ligand 5 (CCL5, also known as RANTES) because these immune markers have been influenced by stimulant exposure in non-human animals (Calipari et al., 2018; Scott Rawls, Personal Communication). Levels of these markers will be determined in a fashion similar to the cardiovascular health markers (e.g., with ELISA at the BAL). Because pregnancy can alter immune function biomarkers, we will conduct urine tests for pregnancy monthly.

To study the effect of cocaine abuse on microbiologic immune factors, we will analyze plasma microbiome pre- and post-treatment. Microbial DNA will be extracted from plasma (Qiagen), and the difference of microbial composition in plasma will be analysed by microbial 16S sequencing. Detailed methods have been described previously (Xu, Sci. Rep. 2018; Zuo, AIDS, 2018). For these assays mL fresh blood will be collected in EDTA-containing tube will be centrifuged for 10 min at 450g. The clear top-phase will be transferred to 1.5mL eppendorf centrifuge tubes and stored at -80C until shipment to the Medical University of South Carolina (MUSC) for analysis. These samples will be de-identified and no patient information beyond an alpha-number code will be shared with MUSC.

To further study the influence of changes in cocaine use on immune biomarkers, in partnership with Temple University, we will analyze IL-17A, IL-8, and CCL2 pre- and post-treatment. Samples will be de-identified and no patient information beyond an alpha-number code will be shared with Temple University. Heparinized blood will be spun down at 800 x g for 10 min at 4°C to separate the RBCs from the plasma; this is what we use to collect plasma from whole blood. The plasma will be stored in 1.5 ml Eppendorf tubes; we will collect 0.5 to 1.0 ml of plasma for our assays. The plasma will be stored at -80°C until shipment to Temple University. Shipments will be done in batches on dry ice, using overnight delivery to ensure that the samples stay frozen.

General Health. General health will be measured with standard laboratory chemistries (i.e., hemogram with differential, c reactive protein, chemistry panel 23, GGT, LDH, lipid panel, phosphorous, troponin, uric acid, cortisol), weight, the Medical items of the ASI and the PROMIS Global Health Scale. The standard laboratory chemistries will be completed through blood draws/urine samples collected at the time points noted below and analyzed at the UK Central Laboratory using commercially available assays. Other measures will be completed at the LHBP using paper-and-pencil questionnaires or electronic questionnaires administered through UK's contract with Qualtrics.

Drug Use. Drug use will be monitored at the LHBP using objective (i.e., urine drug screening; breath CO for smoked tobacco use) and subjective (i.e., self-reported Alcohol/Drug items on the ASI; Timeline Follow Back [TLFB] for amount and recency of COC, tobacco and other drug use; 11 symptom CUD assessment from DSM-5) measures. Urine samples will be collected under observed conditions three times weekly (i.e., Monday, Wednesday and Friday), which will ensure adequate monitoring and detection of COC use as noted above. Urine samples will be tested for the presence of BE with a 300 ng/ml cutoff and for recent use of other drugs of abuse (e.g., cannabis, amphetamine, opioids) using an FDA-approved method for qualitative testing. In order to ensure that urine samples are not adulterated, we will use a specimen validity test strip to determine urine pH and specific gravity as well as the presence of adulterants (Urine Specimen Validity Tests, Craig Medical Distribution Inc., Vista, CA). Qualitative urine tests outcomes will be expressed as percent of weekly drug-negative urine samples across the 12-week trial. CO will be measured using a piCO+ smokerlyzer (Bedfont Inc., Medford, NJ) that yields a numerical measure of breath CO in parts per million.

Psychological Function. Psychological function will be assessed using a battery of standardized questionnaires including the Hamilton Rating Scale for Depression (HAMD), the Saint Mary's Hospital Sleep Questionnaire (SMHSQ), the Barratt Impulsiveness Scale (BIS), the Short Inventory of Problems – Cocaine (SIPC) and Psychiatric items from the ASI. A battery of cognitive tasks will also be completed (see appendix). The battery will consist of tasks that are sensitive to impairments in COC users, including the Go No Go Task, the Balloon Analog Risk task (BART), the Risk Aversion task, the nBack and Delay Discounting for Cocaine and Money. These tasks measure domains central to drug use including inhibitory control, risk taking and attention, respectively. All psychological function measures will be completed at the LHBP using paper-and-pencil questionnaires or electronic questionnaires administered through UK's contract with Qualtrics.

Social Function. Social function will be assessed using items from the ASI (Employment/Support, Legal and Family/Social) as well as the HIV Risk-Taking Behavior Scale (HRBS). All social function measures will be completed at the LHBP using paper-and-pencil questionnaires or electronic questionnaires administered through UK's contract with Qualtrics.

Adverse Events. Study staff at the LHBP will formally query adverse events (AEs) across all typical categories of events including illnesses, hospitalizations and accidents, in order to provide consistent monitoring. It is anticipated that there will be few study-related AEs as the main risks to participation are associated with blood draws for laboratory chemistries and biomarkers and DTH testing. However, all staff who have regular contact with study subjects will be instructed on the need to report to the PI any indication that an AE has occurred. They will be instructed to learn as many details as possible regarding the occurrence of the event. The investigators will review each adverse event as it occurs and record them into a master summary document. The investigative team will review this document monthly or more frequently if adverse events occur at a higher rate than anticipated. Adverse event determinations, such as the timing of reporting, as well as severity, whether the AE was anticipated and the likelihood of the AE being study-related, will be made by the study physician and PI according to the UK Institutional Review Board (IRB) guidelines.

Data Collection Schedule

A table indicating the frequency of data collection for study measures is provided below. The schedule of data collection was determined based on the available literature and in consultation with study team experts.

Study Visits. Assessments will occur at the LHBP, the CSC and/or the Gill Heart Institute as described above. For each visit, subjects will be scheduled to come to the LHBP at approximately 8 AM. They will be informed in advance of the length of the visit and any restrictions (e.g., fasting) in place, depending upon which data collection activities are planned. After arrival at the LHBP, subjects will complete standard sobriety measures, provide an observed urine sample that will be tested for the presence of a range of drugs of abuse, and then complete the battery of measures scheduled for collection at the LHBP. Subjects will then be informed of the qualitative result (i.e., BE-positive or -negative) of their urine test and told how much money will be added to their payment. Next, subjects will meet with the counselor if they are scheduled for individual counseling, and will then be transported to the CSC for a blood draw and other testing, if applicable. On days in which blood will be drawn and/or DTH tests, subjects will be instructed to fast prior to their appointment. After completion of data collection, subjects will be provided with an appointment card for their next visit, paid

with a check and discharged from the LHBP. Blood samples for laboratory chemistries and biomarkers will be transported by nursing staff to the UK Central Laboratory or BAL for storage and subsequent analysis.

Study visits fall into one of three categories: *Baseline*, *Intervention* and *Post Intervention*. *Intervention* visits are subdivided based upon the measures scheduled for completion (Table 1 below). Visits will be categorized as 3 Days/Week (approximately 1 hour each), Weekly (approximately 2 hours each), 4 Week (approximately 3 hours each) and 6 Week (approximately 4 hours). Measures that are scheduled for greater frequency will also occur at the less frequent visits (e.g., each Weekly visit will also include the 3 Days/Week measures), with the exception that measures planned for every 4 weeks will not occur at the 6 Week visit. Post Intervention visits will occur at the intervals specified in the table below for 24 weeks after a subject completes the intervention.

Table 1. Outline of data collection frequency. An X indicates when a test will be done, with the exception of the 12-week intervention, where frequency is described instead. "3 Days/Week" indicates measures that will be completed at each of the three weekly visits made by subjects during the intervention (36 total data points/each). "Weekly" indicates measures that will be completed once per week during the intervention (12 total data points/each). "Weeks 4, 8, 12" indicates measures that will be completed at 4-week intervals during the intervention (three total data points/each). "Weeks 6, 12" indicates measures that will be completed mid-way through and at the end of the intervention (two total data points/each). Week 12 indicates measures that will be completed during the final week of the protocol (one data point/each).

Measure (Domain; CV=Cardiovascular, IM=Immune; PS=Psychosocial)	**Baseline**	**12-Week Intervention***	**4 Weeks Post**	**8 Weeks Post**	**12 Weeks Post**	**24 Weeks Post**
Height (General Health)	X					
Drug Urine Screens (PS)	X	3 Days/Week	X	X	X	X
Pregnancy Screen	X	Weeks 4, 8, 12	X	X	X	X
Weight (General Health)	X	3 Days/Week	X	X	X	X
Breath CO (PS)	X	3 Days/Week	X	X	X	X
Vital Signs (CV)	X	3 Days/Week	X	X	X	X
SMHSQ (PS)	X	3 Days/Week	X	X	X	X
HAMD (PS)	X	Weekly	X	X	X	X
Cognitive Battery (PS)	X	Weekly	X	X	X	X
HRBS (PS)	X	Weekly	X	X	X	X
Adverse Events (General Health)	X	Weekly	X	X	X	X
Biomarkers (CV, IM)	X	Weeks 6, 12	X		X	X
DTH (IM)	X	Weeks 6, 12	X		X	X
ASI (PS)	X	Weeks 4, 8, 12	X	X	X	X
PROMIS (General Health)	X	Weeks 4, 8, 12	X	X	X	X
TLFB (PS)	X	Weeks 4, 8, 12	X	X	X	X
PAT (CV)	X	Week 12	X		X	X
SCID-5 (PS)	X	Week 12	X		X	X
SIPC (PS)	X	Week 12	X		X	X
ECG (CV)	X	Week 12	X		X	X
Microbiome (IM)	X	Week 12				
Additional Biomarkers (IM) for analysis at Temple	X	Week 12				
Lab Chemistries (General Health)	X	Week 12	X		X	X

Subjects will earn $60 for the Baseline visit. Subjects will earn $15 for 3 Days/Week visits, $30 for Weekly visits, $45 for 4 Week visits and $60 for the 6 Week visits, in addition to any payment they receive for their

urine sample outcome. Subjects will earn $60 for each Post Intervention visit. Subjects will also earn $15 for completing a follow up visit to have their DTH response measured 48 hours after their 4, 12 and 24 Week Post visit. To increase completion rates, subjects will receive half of the visit payment (e.g., $30 for the 6 Week visit) at the end of each study visit. The remaining half will be paid upon study completion. If a subject completes all study visits, he or she can earn approximately $1,230 in study payments.

Data Analysis

The statistical significance criterion is $p \leq 0.05$.

Aim 1: To demonstrate that reduced COC use improves physiological and biochemical indicators (i.e., biomarkers) of cardiovascular function. Time-and group-varying weekly number of BE-negative urine samples will be analyzed as the primary predictor of cardiovascular outcomes (e.g., endothelin-1 levels) using generalized linear mixed models (GLMM; Stata 14, College Station, TX). All models will be constructed using intent-to-treat analyses including non-completing subjects, whereby the group to which the participant is randomized will be utilized. GLMM are particularly well suited for analyses of longitudinal data, as they allow for multiple observations over time, correlations among observations within an individual subject, for subjects measured at different time points and for baseline covariates (e.g., sex; age; race) and covariates that change over time (e.g., alcohol use). Although GLMM allow for missing data, any missing data will first be tested to determine whether they are missing at random or missing not at random (MNAR). Any data MNAR will be subject to multiple imputation.

Aim 2: To demonstrate that reduced COC use improves physiological indicators and biomarkers of immune function. Time- and group-varying weekly number of BE-negative urine samples will be analyzed as the primary predictor of immune outcomes (e.g., IL-10 levels) using GLMM. Other details are the same as for cardiovascular outcomes.

Aim 3: To demonstrate that reduced COC use improves psychosocial function. Time-and group-varying weekly number of BE-negative urine samples will be analyzed as the primary predictor of psychosocial outcomes (e.g., other drug use) using GLMM. Other details are the same as for cardiovascular outcomes.

Other Analyses: This study will gather a rich data set of drug use indicators in addition to our primary indicator of weekly number of BE-negative urine samples. As such, analyses with other COC use indicators such as self-report from the TLFB and ASI, along with overall percentage of BE-negative urines and absolute number of BE-negative urines, will also be conducted to evaluate how COC use reductions indicated on those measures produce beneficial health outcomes. Inter-relationships between biomarker and physiological outcomes will be assessed using correlational analyses to determine how biomarker improvements predict physiological improvements from data collected at the same time point (e.g., cardiovascular biomarkers and ECG outcomes from Week 12), as well as from biomarker outcomes that precede physiological assessments (e.g., cardiovascular biomarkers from Week 6 and ECG outcomes from Week 12). Other planned exploratory analyses include comparison of our findings to any available normative data (e.g., lab normal ranges for ranges for CRP) to better demonstrate clinically meaningful improvements produced by COC use, as well as evaluation of reduction thresholds whereby subjects will be grouped based on percentage of BE-negative samples across the trial (i.e., 0-25%, 26-50%, 51-75% and 76-100% negative across the trial).

Sample Size Justification

The physiological and biological cardiovascular function tests will be the primary outcome measures from the intervention and follow up period because cardiovascular insult is one of the most troubling health problems associated with COC use. As such, previously published data regarding the effects of COC use reduction on endothelin-1 levels were used to estimate the necessary sample size for this trial. In that study, reduced COC use significantly reduced endothelin-1 levels (estimated effect size [r]=0.28), approximately half of that observed after COC abstinence. Although cardiovascular measures will be our primary outcome, it is important to note that comparable effect sizes have been observed for indicators of psychosocial outcomes as a function of reduced COC use. Effect sizes observed following COC use reduction in those studies ranged from approximately 0.15 to 0.45 for statistically significant outcomes (e.g., improved ratings of “Good Functioning” after treatment, reduced alcohol use at the end of treatment). Enrolling 66 completing subjects in each group will give us 80% power (alpha=0.05) to detect effect sizes (r) as small as 0.14 when comparing

data across the three groups. This sample size will also allow us to conduct exploratory analyses and control for any relevant biological variables that might influence outcome. Dependent variables are continuous, increasing our power relative to using dichotomous variables.

8. RESOURCES

This study will take place at University of Kentucky LHBP and CSC. Study visits will only be conducted on weekdays, but subjects will be provided with emergency contact information should they experience problems/AEs/SAEs on weekends. The LHBP and CSC are well equipped to conduct the necessary physiological, behavioral and medical assessments. Dr. Hays is an adult psychiatrist who has worked extensively with individuals with substance use disorders in both the clinical and research setting and he is the responsible medical investigator for this study. Dr. Rayapati is a psychiatrist who has worked extensively with individuals with substance use disorders in both the clinical and research setting and he is the back up medical investigator for this study. Dr. Smyth is a cardiologist who has worked extensively with diverse populations in both research and clinical practice—she will be available to consult on cardiovascular screening and experimental results. They will be available to attend to any medical problems. Dr. Stoops will provide scientific oversight for the study and has safely completed numerous human behavioral pharmacology studies and outpatient clinical trials. Overall, the study team and resources described above are well equipped to protect subjects and successfully implement, carry out and complete this study protocol.

9. POTENTIAL RISKS

The behavioral and physiological assessment procedures employed in this study are benign. The primary risks to the subjects are those related to the blood draws, which can lead to fainting, bruising, discomfort or infection, and subcutaneous administration of the candida yeast for the test of cellular mediated immunity, which can lead to inflammation and discomfort.

There is also the risk that others may see a subject's Protected Health Information (PHI). PHI is considered individually identifiable health information transmitted or maintained in any form (electronic means, on paper, or through oral communication) that relates to the past, present or future physical or mental health conditions of an individual that may be used or disclosed. The following PHI will be collected as part of this project: names (individual, employer, relatives, etc.), addresses (individual, employer, relatives, etc.), telephone number, Social Security number (necessary for payment), dates (birth, admission, discharge), medical record numbers, driver's license numbers, mental and physical health history, drug use history, results from mental and physical health screening, results from questionnaires and other experimental measures.

10. SAFETY PRECAUTIONS

Dr. Hays or Rayapati will review screening materials for all potential subjects for physical and psychiatric contraindications to participation and will monitor subjects throughout participation. Participation is voluntary, so individuals can withdraw at any time if they find the study procedures undesirable. To minimize risks of blood draws, standard procedures will be used and universal precautions will be taken to reduce risks of fainting, bruising, infection or discomfort. Subcutaneous candida yeast has been administered safely in intervals similar to that proposed here), however, to minimize risks, subjects that report having compromised immune systems (e.g., organ transplant, AIDS) will not be enrolled in the protocol. Subjects who have experienced extreme hypersensitivity/allergy to candida yeast or similar products will also be excluded.

All subject PHI is confidential and will be protected according to the guidelines established by the Health Information Portability and Accountability Act (HIPAA). An "Authorization to use and disclose PHI for research purposes" approved by the UK IRB will be used. This allows the investigators on this project to use or share health information with the United States Department of Health and Human Services (DHHS) representatives, the UK IRB, the UK Office of Research Integrity (ORI), UK medical center representatives, other research collaborators or when required by law. In addition, a Certificate of Confidentiality will be obtained. Files will not contain the name of the subject. Instead, each subject will be assigned a unique identifying number. All written documents, including PHI, will be stored in locked cabinets at the LHBP. Key access will be limited to immediate laboratory personnel. Electronic information will reside on a stand-alone, password-protected computer. Electronic transmission via e-mail or FAX with subject PHI will have a statement of confidentiality.

During the conduct of this project, we will maintain an active concern for providing proper protection of the welfare and rights of the research subjects.

Legal risks including loss of confidentiality: All intake documentation that contains personal information is handled separately from the actual data collected during the study. All information of a personal nature (intake assessments, medical test results) is kept locked either on password-protected computers or in secure filing cabinets all behind locked doors and accessible only to key personnel involved in the research.

11. BENEFIT vs. RISK

The degree of risk to which individual study subjects are exposed as a consequence of their research participation is low. In contrast, the potential and probable benefits to be derived by society in general and by patients with cocaine use disorder appear to be considerable. The major benefits of this study are scientific and clinical ones related to the knowledge gained concerning the positive effects of reduced cocaine use. Individual study subjects are expected to benefit personally from reduced cocaine use during the treatment protocol; the manualized treatment provided by our Master's or Graduate level counselor; and the medical and psychiatric evaluations and referrals for medical and psychiatric treatment that are provided whenever appropriate. Overall, the risk/benefit ratio appears favorable and the conduct of this research seems well justified.

12. AVAILABLE ALTERNATIVE TREATMENTS

There are no available alternative treatments as widely effective treatments for cocaine use disorders have yet to be identified.

13. RESEARCH MATERIALS, RECORDS AND PRIVACY

Observed urine samples and blood samples will be collected at baseline prior to and during a subject's participation in the experimental protocol. These samples will be tested for the presence of a full range of drugs of abuse, as well as for biomarkers and routine screening outcomes (e.g., liver function). Other data obtained from the subjects will involve subject responses on questionnaires, various computer-based performance tasks and non-intrusive staff observations and ratings. The consent form states that subject's confidentiality will be protected.

14. CONFIDENTIALITY

Identifying information will be stored in a separate, locked area from all other de-identified data and codes linking the two will be kept under lock and key or on password protected computers. Incidental materials containing subject identifiers will be shredded or incinerated. Identification and access of identified data/specimens will be available only to study investigators when it is detrimental to subject safety or the conduct of the research protocol. For example, if a subject has an adverse event, we will want to obtain a quantitative drug screen to identify whether there may have been illicit drug use while in the study versus a true adverse event related to the study procedures. In the future, data/specimens may be shared with non-UK affiliations in a HIPAA compliant manner.

15. PAYMENT

In total, subjects can earn $1980 in the high value group and $468 in the low value group if they are completely abstinent throughout the trial, although this is unlikely given previous findings. Subjects assigned to the control condition will receive $13 per urine sample they provide independent of test results. Subjects will earn $15 for 3 Days/Week visits, $30 for Weekly visits, $45 for 4 Week visits and $60 for the 6 Week visits, in addition to any payment they receive for their urine sample outcome. Subjects will earn $60 for each full Post Intervention visit and $15 for visits in which their DTH response is evaluated (i.e., follow up visits 48 hours after the 4, 12 and 24 Weeks Post Intervention visit; these visits are expected to last 30-60 minutes). To increase completion rates, subjects will receive half of the visit payment (e.g., $30 for the 6 Week visit) at the end of each study visit. The remaining half will be paid upon study completion. If a subject completes all study visits, he or she can earn approximately $1,230 in study payments.

16. COSTS TO SUBJECTS

Subjects will be responsible for costs of transportation to and from the laboratory for scheduled appointments. Costs for the screening and research procedures will be paid by the LHBP.

17. DATA AND SAFETY MONITORING

The purpose of this study is to demonstrate the beneficial effects of reduced cocaine use. Completing subjects will be 198 men and women of various races/ethnicities, aged 18 to 65 who meet DSM-5 criteria for moderate-severe cocaine use disorder. Only subjects that are seeking treatment for their drug use will be

eligible for this study. This sample will be recruited from the local community and will participate as outpatients for approximately 36 weeks.

The PI, William W. Stoops Ph.D., and the primary study physician, Lon R. Hays, M.D., M.B.A. will be responsible for monitoring the safety and efficacy of this trial, executing the DSMP and complying with the reporting requirements. Susan S. Smyth, M.D., Ph.D. will also contribute to safety monitoring, consulting with Dr. Hays regarding cardiovascular outcomes as needed. The PI will provide a summary of the DSM report to NIDA on an annual basis as part of the progress report. The DSM report will include the subjects' sociodemographic characteristics, expected versus actual recruitment rates, retention rates, any quality assurance or regulatory issues that occurred during the past year, summary of adverse events (AEs) and serious adverse events (SAEs) and any actions or changes with respect to the protocol. The DSM report to NIDA will also include, if applicable, the results of any efficacy data analysis conducted.

Data Monitoring Plan. Data will be collected using a computerized data collection and management system wherever possible. This system automates the collection of data, which ensures the accuracy and completeness of data collection. The data are stored in a unique file on the hard drive of the computer and are printed after all the tasks are completed. In all instances, the data files do not contain the name of the subject, but instead, a unique four-digit number identifies each subject. A computer file linking the unique number with the subject's name will be kept on a stand-alone, password-protected computer. All data requiring hand entry (e.g., cardiovascular measures, laboratory chemistry outcomes) will be double entered by two separate staff members and comparison macros run to ensure accuracy. Data files for all outcomes will be combined into a single electronic spreadsheet for each subject by the PI. Data for all subjects will then be combined into a single electronic spreadsheet and separated by experimental measure for statistical analysis by Jennifer Havens, Ph.D., M.P.H.

The primary outcome measure in this study will be the influence of reduced cocaine use on endothelin-1 levels. Secondary outcome measures include other cardiovascular, immune and psychosocial function. Data will be analyzed as described in the research plan. The alpha level will be set at 5%.

As noted above, wherever possible, data are collected using an automated computer system, which increases the accuracy and completeness of data collection and ensures the validity and integrity of the data. The quality of data analyses will be monitored by random inspection by the PI and/or Co-Investigators.

Safety Monitoring Plan. Potential subjects will provide information regarding their drug use history and undergo an extensive physical and psychiatric health screening to determine their eligibility and safety of their participation. Potential subjects must meet DSM-5 criteria for moderate-severe cocaine use disorder and must present with a urine sample positive for cocaine/benzoylecgonine at the time of screening. Any potential subject with poor venous access, self-disclosed compromised immune function or who has experienced an allergic reaction to candida yeast or similar products will be excluded. Methods for monitoring adverse events (AEs) will include observations by the medical and research staff, spontaneous report by the subjects and regular measures of physiological function.

All AEs occurring during the course of each study will be collected, documented and reported to the PI and physician co-investigators. The occurrence of AEs will be assessed for the duration of participation and during the follow up visits at 2 and 4 weeks following study completion. Each week a study investigator will review the AE forms from the previous week for events that were reported as new or continuing. The study investigators will follow all AEs to the point of a satisfactory resolution. Subjects may be withdrawn from the study if the medically responsible investigator (i.e., Dr. Hays, in consultation with Dr. Smyth if applicable) determines it is the best decision in order to protect the safety of the subject. All AEs will be assessed to determine if they meet criteria for a serious adverse event (SAE).

Serious Adverse Events, as defined by the FDA, will be systematically evaluated for the duration of participation and during the follow up visits at 2 and 4 weeks following study completion. Any SAE, whether or not related to the study, will be reported to the IRB, NIDA and the FDA. The initial SAE report will be followed by submission of a completed SAE report to all three organizations.

In the event that a subject either withdraws from a study or an investigator decides to discontinue a subject due to an SAE, the subject will have appropriate follow up medical monitoring as directed by Dr. Hays and Dr. Smyth. Monitoring will continue until the problem requiring hospitalization has resolved or stabilized with no

further change expected, is clearly unrelated to the study intervention or results in death. Outcome of SAEs will be periodically reported to NIDA. A summary of the SAEs that occurred during the previous year will be included in the annual progress report to NIDA.

19. RESEARCH INVOLVING NON-ENGLISH SPEAKING SUBJECTS OR SUBJECTS FROM A FOREIGN CULTURE Not applicable.

20. HIV/AIDS RESEARCH POLICY Not applicable.

21. PI SPONSORED FDA-REGULATED RESEARCH Not applicable.

Appendix- Task Descriptions

The Go/NoGo task is a computer-administered task that is delivered by scripts written in either E-Prime or Presentation software. The Go/NoGo task requires a single response to Go stimuli and a response withhold to NoGo stimuli. Go stimuli are presented more frequently than the NoGo stimuli so that the participant develops a (prepotent) tendency toward response execution.

The Balloon Analogue Risk Task (BART) is a computerized, laboratory-based test of risky behavior, which can be used with adolescents and adults. During the test, participants inflate, or pump up, a hypothetical balloon. Participants receive a certain amount of money for each pump of the balloon until it pops, at which point all money is lost. Participants can stop inflating the balloon at any point in the trial and collect the accrued money. Unlike other decision tasks that elicit choices between different discrete response options (with different scheduled penalty probabilities), the penalty probability in the Balloon Analogue Risk Task accelerates as a function of reward pursuit within the *same* behavioral option (such as alcohol drinking).

n-Back. The n-Back task will be used to measure working memory and working memory capacity (Jaeggi et al. 2010). In this task, subjects are presented with a sequence of numbers and asked to indicate when the current stimulus matches the one from "n" steps earlier. Two settings will be used in this study, the 1-back and the 2-back (i.e., matching 1 and 2 stimuli back, respectively). The primary outcome of this task is the percentage of correct responses.

Hypothetical Delay Discounting. A 5-trial adjusting delay discounting task will be used to rapidly assess discounting rates for various commodities (Koffarnus and Bickel, 2014). In this task, subjects making a series of 5 choices between an immediately available, smaller reinforcer and a larger reinforcer at various delays. Versions of this task with monetary (e.g., $1000 delayed versus $500 now) and cocaine (e.g., $1000 of cocaine delayed versus $500 of cocaine now) commodities will be used. Subjects will be told that all choices are hypothetical. The primary outcome of this task is the discounting rate (k). Previous research has demonstrated that this measure provides rapid and accurate discounting rates across a range of commodities (Cox and Dallery, 2016; Koffarnus and Bickel, 2014; Strickland et al., 2017).

Risk Aversion Task. A risk aversion task will be used to assess general aversion towards outcome variability regardless of if that outcome is a loss or a gain (De Martino, Camerer, & Adolphs, 2010). This task presents subjects with a series of monetary gambles of gain only. Each gamble consists of the choice to keep a sure amount or flip a coin for double or nothing. The task consists of 11 trials and includes the following monetary values: $2, 5, 10, 15, 20, 25, 30, 35, 40, 45, and 50. None of the gambles will be actualized.