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IRBNet #1617313 (ProSPECT #00002689)

Electrophysiological Predictors and Indicators of Contingency Management Treatment Response

Funding Agency: VA ORD

Principal Investigator: Stuart Steinhauer, PhD[1]

Version Date: 06-02-25

[1] Dr. Steinhauer is the custodial PI following departure of the original PI (Dr. Sarah Forster) from VA Service.

NOTE: This is the protocol document approved by the VA Pittsburgh Healthcare System Institutional Review Board. Formatting of this document reflects the original protocol management system (ProSPECT) in which the submission was developed.

Study Identification Information

1.0 * Study Name:

Electrophysiological Predictors and Indicators of Contingency Management Treatment Response

2.0

* Brief Description (using layman's terms) - 500 words or less:

Electrophysiological methods, including event-related potential and functional connectivity approaches, have potential to clarify mechanisms of substance use treatment response and characterize individual differences therein. Veterans are disproportionately affected by disorders of addiction, of which cocaine use disorder (CUD) is particularly problematic due to high relapse rates and the absence of approved pharmacotherapy options. Behavioral interventions for CUD have therefore become an important focus and Contingency Management (CM) has emerged as the best-supported approach. CM involves reinforcing cocaine abstinence (established through objective testing) with reliable, short-term reward, such as chances to win prizes (i.e., Prize-Based CM or PBCM). Given robust empirical support, nationwide dissemination of PBCM has been supported by a VHA initiative since 2011. However, PBCM response rates are variable and long-term benefits are limited – problems magnified by the cost of implementation with respect to staffing and prizes. Measurement-based approaches to PBCM implementation have promise to improve the effectiveness and efficiency of CM programming but have not yet been investigated within the VA or considered in relation to promising neuromarkers. Importantly, two versions of PBCM are already utilized at VA sites and may differentially benefit individuals with distinct neurocognitive profiles. Specifically, VA PBCM programs employ either abstract (voucher prize) or concrete (tangible prize) incentives, the latter of which may more effectively incentivize abstinence in Veterans with poor future-oriented thinking and planning ability. While selection between existing PBCM variants currently reflects practical considerations only, pretreatment neurocognitive functioning could meaningfully and realistically inform clinical decision-making in this regard. A sample of healthy controls will also be recruited for evaluation and serve as a comparison group to evaluate the differences between the treatment-seeking CUD sample and the healthy veteran sample.

This project aims to advance measurement-based implementation of CM by testing a novel neurocognitive model with immediate implications for the use of abstract versus concrete PBCM incentives within the VA. Specifically, the future-minded decision-making (FMDM) model posits that CM scaffolds future-oriented goal representation and self-control to support abstinence during in the moment use-related decision-making. For individuals with greater FMDM impairment, concrete, readily-accessible incentives may be more effective than abstract voucher-based rewards (which require future-oriented thinking and planning to acquire value). To test this model, neurocognitive substrates of FMDM will be examined as predictors of differential treatment response in voucher (VoucherPBCM) versus tangible prize (TangiblePBCM) versions of PBCM. Veterans with CUD will be allocated to VoucherPBCM or TangiblePBCM, and followed for a 12-week treatment interval. Pre- and post-treatment

electroencephalography (EEG) and cognitive-behavioral assessments will be used to measure FMDM-related constructs (working memory, self-control, future-oriented decision-making, future reward representation) and related neuromarkers. These measures will be investigated as predictors of differential treatment response in VoucherPBCM versus TangiblePBCM, as well as maintenance of gains during a post-treatment follow-up period. Change in FMDM-related neural and cognitive measures over the course of treatment will also be evaluated for evidence of neuroadaptation (e.g., changes in functional connectivity) and enhancement of FMDM function through PBCM. Taken together, results of the current research project will represent a first step toward precision implementation of CM within the VA.

3.0 * Is this research study a Greater than Minimal Risk Clinical Trial? Yes **No**

4.0 * Is this study a Greater than Minimal Risk Comparative Effectiveness research? Yes **No**

5.0 * Principal Investigator:

Stuart Steinhauer, PhD (custodial PI)

View: 1.0 Study Identification Information

Study Identification Information (Continued)

1.0

* Do you certify that all research staff administering informed consent are knowledgeable about the study?

yes

2.0

* To the best of your knowledge do you, or any member of your research staff, have any potential, actual or perceived conflict of interest of a professional or personal nature that may affect any aspect of the research, including, but not limited to, the review and/or conduct of this study?

Yes No

If yes, provide a description, including name of study team member with conflict:

Dr. Steinhauer is a member of IRB1 and IRB2.

3.0 * Qualifications of the Investigators:

Stuart Steinhauer, PhD., VA Mentor/Principal Investigator (2.4 cal mos, GS 14/9, 5/8th VA).

Dr. Steinhauer is a VAPHS Research Health Scientist and Adjunct Research Associate Professor of Psychiatry at the University of Pittsburgh. He additionally serves as the Director of the Biometrics Research Program at VAPHS and the University of Pittsburgh, Department of Psychiatry, including the Biometrics Research Laboratory at VAPHS where the proposed work will take place. Dr. Steinhauer is a renowned expert on psychophysiology with over three decades of VA research and mentorship experience and will serve as Dr. Forster's primary mentor on the proposed work. Dr. Steinhauer has overseen Dr. Forster's training throughout the award period and provided regular guidance on implementation of all planned research activities, as well as quality assessment, management, and analysis of all resulting data. As Dr. Forster has recently transitioned to a non-VA position, Dr. Steinhauer will assume the role of PI for the remainder of the award period. Recruitment for the study has already concluded, so remaining activities to be overseen by Dr. Steinhauer will center around final data collection, data analysis, and study closure.

Sarah Forster, PhD., VA Mentee/Co-Investigator, (2.4 cal mos, GS 11/1, 2/8th VA). Dr. Forster has directly overseen all aspects of the proposed research and received specialized career development training throughout the funding period. Her responsibilities with respect to the current research have included oversight of all participant recruitment, participant enrollment and retention, administration of research assessments, intervention delivery, data collection and management, data analysis, and dissemination of findings. She was also responsible for hiring, training, and direct supervision of all research personnel. Dr. Forster has previously committed 75% effort on the current project and 25% effort in clinical activities through the Behavioral Health Service Line at VA Pittsburgh Healthcare System. Dr. Forster is a licensed clinical psychologist and has over fourteen years of relevant research experience. Dr. Forster has recently transitioned to a non-VA position and will no longer be able to serve as PI for the remainder of the award period, but will continue on as a Co-I.

View: 1.2 VA Involvement

VA Involvement

1.0

Does the proposed research involve any of the following?:

Name

X VA Funding
X VA Personnel Funded Effort
X VA Patients or their Private Health Information
Other VA Resources: Central IRB
X Other VA Resources: VA Equipment
X Other VA Resources: VA Property (Including space leased to, or used by VA)
X Other VA Resources: VA Databases
None of the Above apply to this research

View: 1.3 Study Funding Information

Study Funding Information

1.0

* Funding Sources:
Funding Source (Other) Code

Clinical Science R&D (9050): VA Career Development Award
Veterans Research Foundation of Pittsburgh (VRFP):Gerald Goldstein Early Career Mental Health Research Award

2.0

Upload Grant Application, if applicable (If NIH, VA, voluntary agency, must upload):

Name Modified Date

CDA Required Sections 9/27/2018 11:03 AM
Forster CDA Research Plan 7/11/2019 2:41 PM
Goldstein Award 1/7/2021 11:21 AM

View: 1.4 Resources

1.0

* Do you currently have adequate resources (e.g., staff, physical space, information technology, etc.) to protect the safety of participants, staff, and the confidentiality of subjects' data during the conduct of this study?

Yes No

If yes, include a listing of the VAPHS resources that will be used for this study and are necessary to protect participants.

Dr. Steinhauer is the Director of the Biometrics Research Program and has provided Dr. Forster with 150 sq ft of laboratory space at the Research Office Building of the VAPHS University Drive Campus in order to conduct the current project. This lab space has been outfitted with equipment for the acquisition and analysis of electroencephalographic (EEG), pupillometry, and cognitive-behavioral (e.g., response time and accuracy) data, as well as presentation of experimental stimuli such as images and sounds. Updated equipment has additionally been purchased using funds from the current award. A larger laboratory space (~300 sq ft) is also available for our use and equipment may be migrated to this location, when necessary. Drs. Forster and Steinhauer also have office space and access to Dell workstations at the Research Office Building that can be used for data management and miscellaneous study duties. Also available at the Research Office Building are several interview/treatment rooms that may be used for the informed consent process, as well as collection of self-report and interview data and administration of treatment and check-in sessions, as needed. Facilities are also available for the acquisition, testing,

and disposal of urine and saliva specimens that will be acquired to screen for recent substance use. Our budget includes funds for personal protective equipment and related supplies involved in the safe handling and disposal of urine and saliva specimens.

Contingency Management (CM) is offered through the Center for the Treatment of Addictive Disorders at VA Pittsburgh Healthcare System. Dr. Forster has served as the local implementation coordinator for CM in consultation with the VHA National CM Implementation team and head of this effort, Dr. Dominic DePhilippis of the Philadelphia CESATE. Office and storage space in Building 29 will be available for treatment delivery and necessary supplies for CM delivery are available or will be purchased with study funds. The team leader of CTAD and VISN 4 SUD Lead, Dr. Leigh Gemmell, has provided a letter of support for the proposed work (see Section 15: Miscellaneous Documents). It is further noted that investigators will have access to the study population through recruitment mechanism described in the protocol and feasibility of recruitment has already been demonstrated in a separate pilot project (Pro1787). A letter of support has been provided by the Behavioral Health service line.

If no, please describe the resources that will be needed and explain how the resources will be obtained before the study is initiated:

2.0 * VAPHS requires that either the PI or co-PI have a physical presence at VAPHS. Please describe the role the PI and/or co-PI have at VAPHS with respect to clinical responsibilities or in relation to other research activities.

The original PI (Forster) was an 8/8 Research Health Science Specialist at VAPHS from 1/2019-10/2023. The current PI (Steinhauer) maintained a 5/8 Research Health Science Specialist position at VAPHS throughout the remainder of the active award period. Both Drs. Steinhauer and Forster continue to maintain a physical presence at VAPHS, where Dr. Steinhauer maintains his position as Director of the Biometrics Research Program and Dr. Forster maintains a Without Compensation (WOC) appointment.

3.0 * Will off-site ancillary service facilities (e.g., radiology services, central labs, non VA space, etc) be used for this study?

Yes **No**

If yes, please provide the location and a brief description of the project activities to be conducted at the off-site ancillary facilities:

4.0 * Will a firm be contracted to obtain consent from subjects, collect private individually identifiable information from human subjects, or be involved in activities that would institutionally engage the firm in human subjects' research?

Yes **No**

If yes, please provide a description of the contracted service(s):

* Please specify the IRB that has oversight of the firm's activity(ies):

Name of Site / Institution IRB Approval Document FWA Number

There are no items to display

5.0 Collaborations

Please list any non-VAPHS institutions or individuals (i.e. co-authors, mentors, etc.) that you will collaborate with and describe their specific role in the research:

The following individuals will serve as collaborators and will not have access to data. Drs. Dickey and Siegle may view results of the study in aggregate form. Other collaborators will provide consultation and training without access to study data in aggregate or non-aggregate form.

Michael Walsh Dickey, PhD., VA Co-Mentor (0.6 cal mos, GS 13/7, 5/8th VA). Dr. Dickey is a VAPHS Geriatric Research, Education, and Clinical Center Research Scientist at VAPHS, as well as an Associate Professor of Psychology and Communication Science and Disorders at the University of Pittsburgh. Dr. Dickey will oversee Dr. Forster's training in the area of neuroadaptive processes underlying cognitive recovery, as well as application of this knowledge to develop future directions of the proposed work. He will also work with Dr. Forster to conduct exploratory longitudinal analyses using mixed effects modeling to evaluate interrelationships between multivariate treatment outcomes (e.g., neurocognitive recovery vis-à-vis changes in substance use over time).

Greg Siegle, PhD., Non-VA Mentor. Dr. Siegle is an Associate Professor of Psychology and Psychiatry at the University of Pittsburgh with expertise in EEG, functional connectivity analysis, neuropredictive analytics, and longitudinal analysis of biological signals. He will oversee Dr. Forster's training in these areas and will additionally assist Dr. Forster in setting up new lab equipment and optimizing data quality. Dr. Siegle will provide guidance on implementation of functional connectivity analyses and will work with Dr. Forster to improve the translational potential of predictive modeling aims, as well as future directions of the proposed work.

Dominick DePhilippis, PhD., Contingency Management Consultant. Dr. DePhilippis is the Education Coordinator for the Center of Excellence in Substance Addiction Treatment and Education (CESATE) at the Corporal Michael J. Crescenz VA Medical Center and Director of the VHA Contingency Management Sustainability Incentive Program. Dr. DePhilippis will provide consultation on clinical implementation of Contingency Management at VA Pittsburgh Healthcare system to ensure high-fidelity delivery of the intervention in the proposed work.

William Cohen, PhD., Machine Learning Consultant. Dr. Cohen is a Director of Research & Engineering at Google AI. He will provide consultation on the machine learning research and training aims of the proposed work. Specifically, Dr. Cohen will work with Dr. Forster to develop predictive models based on prospective clinical outcome data from the proposed work using Classification and Regression Tress, Random Forests, and Tabu Regression methods.

William Hetrick, PhD., Functional Connectivity Consultant. Dr. Hetrick is a professor in the Department of Psychological and Brain Sciences at Indiana University and also serves as chair of this department. Dr.

Hetrick will host Dr. Forster at the Clinical and Cognitive Neuroscience Center at Indiana University to conduct week-long hands-on training sessions in functional connectivity analysis.

Dae-Jin Kim, PhD., Functional Connectivity Consultant. Dr. Kim is a research scientist in the Computational Cognitive Neuroscience Laboratory and Clinical and Cognitive Neuroscience Center at Indiana University. He will train Dr. Forster on computation of the synchronization likelihood metric of functional connectivity which will be utilized to quantify coordination of EEG brain signals across electrode sites.

Olaf Sporns, PhD., Functional Connectivity Consultant. Dr. Sporns is a distinguished professor in the Department of Psychological and Brain Sciences at Indiana University, as well as the director of the Computational Cognitive Neuroscience Laboratory at that institution. Dr. Sporns will train Dr. Forster on graph theoretic analysis of EEG data in order to achieve exploratory aims of the proposed work.

5.1

If this is not Multi-Site Research, please upload the appropriate written agreement(s) here:

Name

There are no items to display

View: 1.5 Project Information

1.0

Does the project involve any of the following (check all that apply):

Biological Hazards (including human biological specimens) X
Chemicals X
Ionizing radiation or use of radioactive materials
Drug, Biological, or Nutritional (e.g. herbal or dietary) Supplement

2.0

Project Focus (check if applicable):

Traumatic Brain Injury (TBI)
Post Traumatic/Post Deployment Stress Disorder (PTSD/PDSD)
Operation Iraqi Freedom/Operation Enduring Freedom (OIF/OEF)

3.0

KEYWORDS

Please provide a minimum of 3, maximum of 6 keywords. Please use MeSH terms.

* Behavior, Addictive

* Electroencephalography

* Decision Making

Reinforcement (Psychology)

Clinical Decision-Making

Self-Control

4.0 * Please describe the type of study:

The proposed work will utilize a prospective Phase III clinical trial design to identify patient-level predictors of treatment outcome in TangiblePBCM versus VoucherPBCM (Specific Aim 1) and evaluate longitudinal recovery of FMDM function in TangiblePBCM and VoucherPBCM in order to clarify mechanisms of CM treatment response (Specific Aim 2). This Class III study will employ stratified random assignment into one of two subgroups: (1) 12 weeks of TangiblePBCM (n = 70) or(2) 12 weeks of VoucherPBCM (n = 70),. As CM is an adjunctive treatment option, it is noted that patients in both CM groups will also experience TAU during the CM treatment interval (i.e., PBCM = PBCM + TAU). CM recipients will additionally be followed for 6 months post treatment. Importantly, the proposed design enables evaluation of CM outcome predictors within a total sample of 140 CM recipients – both with respect to initial treatment response and longer term (6 month post-treatment outcomes Participants will receive a Baseline Assessment prior to the initial 12 Week Treatment interval (TangiblePBCM or VoucherPBCM), as well as a Follow-up Assessment at the conclusion of this period. Data from Baseline and Follow-up Assessments will enable longitudinal analysis of treatment-related change in EEG and cognitive-behavioral measures in TangiblePBCM and VoucherPBCM. For all CM recipients, CM treatment data (i.e., attendance, urinalysis results, prize outcomes) will be monitored throughout the 12 Week treatment interval. Substance use during the treatment interval will additionally be monitored for all participants (i.e., CM) through weekly self-report measures and urine-based drug tests; outpatient treatment engagement will be quantified on the basis of chart review. For CM recipients, treatment engagement and self-reported substance use will additionally be followed on a monthly basis for 6 months post-treatment. This design therefore provides for quantification of CM treatment response and long-term outcomes for both TangiblePBCM and VoucherPBCM subgroups. Pre-treatment predictors of CM treatment response and long-term outcomes can therefore be evaluated for all CM recipients (n = 140) by including treatment condition (TangiblePBCM versus VoucherPBCM) as an explanatory variable to parse condition-specific predictors.

A sample of healthy controls, who either do not have a history of substance use treatment or have been in recovery for ≥1 year, will also be recruited as a comparison group.

5.0 * Will any of the research being conducted as a part of this study be used to fulfill academic requirements (e.g., master's thesis, dissertation, or other academic program requirements necessary to obtain a degree/certification, etc.)? Yes **No**

View: 1.6 (CR) Study Locations

Study Locations

1.0

* Please add the local sites where this study will be conducted:

Location

View VAPHS University Drive Division

If Other, Please Specify:

View: 1.6.1 (CR) Multi-Site Study

1.6.1 Multi-Site Study

1.0 * Is this a multi-site study:

Yes **No**

View: 1.7 Section Chief and Service Line VP approvals

Please upload the approval of the Section Chief, if applicable and the Service Line VP.

1.0 * Institutional Approval Document:

PART I (0.04)

View: 2 Study Objectives & Design

Study Summary

1.0 Funding End Date:

1/1/2024

2.0

* Abstract. Please provide a brief description of the study.

Electrophysiological methods, including event-related potential and functional connectivity approaches, have potential to clarify mechanisms of substance use treatment response and characterize individual differences therein. Veterans are disproportionately affected by disorders of addiction, of which cocaine use disorder (CUD) is particularly problematic due to high relapse rates and the absence of approved pharmacotherapy options. Behavioral interventions for CUD have therefore become an important focus and Contingency Management (CM) has emerged as the best-supported approach. CM involves reinforcing cocaine abstinence (established through objective testing) with reliable, short-term reward, such as chances to win prizes (i.e., Prize-Based CM or PBCM). Given robust empirical support, nationwide dissemination of PBCM has been supported by a VHA initiative since 2011. However, PBCM response rates are variable and long-term benefits are limited – problems magnified by the cost of implementation with respect to staffing and prizes. Measurement-based approaches to PBCM implementation have promise to improve the effectiveness and efficiency of CM programming but have not yet been investigated within the VA or considered in relation to promising neuromarkers. Importantly, two versions of PBCM are already utilized at VA sites and may differentially benefit individuals with distinct neurocognitive profiles. Specifically, VA PBCM programs employ either abstract (voucher prize) or concrete (tangible prize) incentives, the latter of which may more effectively incentivize abstinence in Veterans with poor future-oriented thinking and planning ability. While selection between existing PBCM variants currently reflects practical considerations only, pretreatment neurocognitive functioning could meaningfully and realistically inform clinical decision-making in this regard.

This project aims to advance measurement-based implementation of CM by testing a novel neurocognitive model with immediate implications for the use of abstract versus concrete PBCM incentives within the VA. Specifically, the future-minded decision-making (FMDM) model posits that CM scaffolds future-oriented goal representation and self-control to support abstinence during in the moment use-related decision-making. For individuals with greater FMDM impairment, concrete, readily-accessible incentives may be more effective than abstract voucher-based rewards (which require future-oriented thinking and planning to acquire value). To test this model, neurocognitive substrates of FMDM will be examined as predictors of differential treatment response in voucher (VoucherPBCM) versus tangible prize (TangiblePBCM) versions of PBCM. Veterans with CUD will be allocated to VoucherPBCM or TangiblePBCM conditions and followed for a 12-week treatment interval. Pre- and post-treatment electroencephalography (EEG) and cognitive-behavioral assessments will be used to measure FMDM-related constructs (working memory, self-control, future-oriented decision-making, future reward representation) and related neuromarkers. These measures will be investigated as predictors of differential treatment response in VoucherPBCM versus TangiblePBCM, as well as maintenance of gains during a post-treatment follow-up period. Change in FMDM-related neural and cognitive measures over the course of treatment will also be evaluated for evidence of neuroadaptation (e.g., changes in functional connectivity) and enhancement of FMDM function through PBCM. Taken together, results of the current research project will represent a first step toward precision implementation of CM within the VA. A sample of healthy controls will also be recruited as a comparison group.

3.0 * Describe the study objectives. Please include primary aim and hypothesis, if applicable any secondary aims and hypotheses.

Veterans are disproportionately affected by addictive disorders [1,2] and these conditions increase the likelihood of homelessness, hospitalization, incarceration, and premature death [3-5]. Rising rates have further been reported amongst returning OEF/OIF/OND service members – with nearly one in five diagnosed with a drug use disorder [6]. Cocaine use disorder (CUD) is prevalent [7] and has been associated with poorer treatment outcomes in other high-priority mental health conditions affecting Veterans (e.g., opioid use disorder and PTSD) [8-12], with which CUD frequently co-occurs. Unfortunately, the absence of approved pharmacotherapy options for CUD makes treatment engagement and relapse prevention particularly challenging. In order to improve CUD treatment options, in 2011 the VHA announced the national rollout of Contingency Management (CM) [13,14] – an empirically-supported behavioral intervention offering incentives (e.g., opportunities to win prizes) for negative urine drug screens to reinforce abstinence over a 12-week period. However, while the evidence base for CM is strong, individual responses to CM are variable [15] and long-term outcomes remain poor [16]. Improving the effectiveness of VA CM programming would achieve sweeping benefits for Veterans but demands clarification of mechanisms and predictors underlying CM treatment response. In particular, this knowledge will enable measurement-based adaptation of CM treatment parameters to better meet individual patient needs. This approach has already demonstrated promise [17] and is poised for rapid translation into clinical settings – although previous work has focused on customizing the magnitude and probability of CM reinforcement and this may engender ethical and pragmatic barriers to implementation. Fortunately, a recently proposed future-minded decision-making (FMDM) account of CM [18,19] highlights additional reinforcement parameters (e.g., tangibility of future reward), as well as cognitive components of the intervention that may be more suitable for measurement-based adaptation. According to the FMDM account, CM fosters representation of recovery-related goals in working memory (e.g., future abstinence-contingent reward) to potentiate inhibitory control during in the moment use-related decision-making. Critically, individuals with more profound FMDM deficits may require stronger scaffolding of future reward representation – for example, by providing concrete rather than abstract monetary incentives. This may have immediate implications for CM implementation throughout the VA, wherein a prize-based, intermittent reinforcement version of CM (PBCM) is used with either voucher-based (VoucherPBCM) or tangible object-based (TangiblePBCM) incentives. The FMDM model additionally suggests that CM may actively remediate the cognitive abilities underlying FMDM and strengthening this mechanism of action may further enhance and prolong benefits. Treatment-related neuroadaptation in the context of CM may therefore clarify new opportunities for customization and augmentation of existing programming, but has not yet been well-characterized.

The proposed work will test key predictions of the FMDM account of CM with implications for (1) improved treatment effectiveness and (2) targeted treatment delivery. Individuals with CUD (n=140) will be recruited upon engagement with outpatient substance use services and assigned to 12 weeks of TangiblePBCM (n=70) or VoucherPBCM (n=70). Participants in all conditions will complete EEG and cognitive-behavioral assessments of core FMDM constructs (i.e., goal-informed cognitive control processes, executive working memory, episodic future thinking, and reward anticipation) before and after the 12 week treatment interval. Self-report measures of other clinically-relevant indicators (e.g., addiction propensity and severity, motivation, self-efficacy) will also be evaluated and outcomes (treatment engagement, subjective and objective measures of substance use) will additionally be

followed throughout the 12 week treatment interval and for 6 months post-treatment in both CM groups. Aims and hypotheses are as follows:

Specific Aim 1: Evaluate the utility of EEG and cognitive-behavioral measures of FMDM as predictors of differential treatment outcomes in TangiblePBCM versus VoucherPBCM.

Hypothesis 1a. FMDM-related measures will predict differential outcomes in TangiblePBCM relative to VoucherPBCM, with more FMDM-impaired individuals demonstrating improved treatment response in the former relative to the latter.

Hypothesis 1b. Inclusion of predictors from the FMDM account will significantly improve performance of predictive models forecasting short- and long-term outcomes in CM and inclusion of these predictors will be robust to model-based constraints favoring variables with lower measurement costs.

Specific Aim 2: Evaluate treatment-related change in EEG and cognitive-behavioral correlates of FMDM-related cognitive functioning during CM.

Hypothesis 2a. Individuals who reliably engage in TangiblePBCM and VoucherPBCM will demonstrate greater treatment-related change in functional connectivity networks underlying goal-informed cognitive control processes, as well as behavioral measures of working memory and future-oriented decision-making, relative to individuals who demonstrate poor PBCM adherence.

Exploratory Sub-Aim. Longitudinal change in FMDM-related measures will be investigated in relation to patterns of abstinence during PBCM and will reflect distinct treatment response trajectories.

4.0 * Provide a summary of the background of the study, and explain how this research will contribute to existing knowledge. Describe previous studies that provides a basis to show that the proposed research can be carried out without undue risk to human subjects.

Background

Veterans are disproportionately affected by substance use disorders [1,2] – placing those who have served at an increased risk of homelessness, hospitalization, incarceration, and preventable death [3-5]. Taken together, costs associated with substance use-related healthcare, loss of productivity, and criminality amount to an annual economic burden of 510 billion dollars in the U.S. [20] – largely due to the chronic, relapsing timecourse of addiction. Indeed, over half of Veterans with substance use disorders will have a use-related inpatient hospitalization within one year of treatment [21]. Rising rates of substance use have further been noted amongst OEF/OIF/OND service members, with an estimated 5-18% of OEF/OIF veterans meeting past year criteria for a drug use disorder [6,22]. Overall, the prevalence and chronicity of addictive disorders amongst Veterans translates into a high demand for substance use treatment within the VA, amounting to an estimated cost of 350 million dollars each year – 60% of which supports specialty outpatient care [23].

While the increasing frequency of opioid use disorders amongst Veterans [24] has demanded national attention in recent years, cocaine addiction has been prevalent and problematic for decades, with a relapse rate higher than most illicit drugs [25,26]. Cocaine use disorder (CUD) additionally complicates

treatment of common psychiatric and substance use comorbidities in Veterans – predicting poorer outcomes in individuals with post-traumatic stress disorder, schizophrenia, opioid use disorder, and traumatic brain injury [8-12]. Unfortunately, while effective treatment of CUD is a clear priority for VHA, the absence of FDA-approved pharmacotherapy options for cocaine users has made successful treatment engagement and relapse prevention particularly challenging. Without medications to support abstinence, providers have increasingly embraced specialized behavioral interventions for CUD; of which, Contingency Management (CM) has emerged as the frontline, empirically-supported treatment option (when used as an adjunct to treatment-as-usual (TAU) outpatient care).

In line with VA's commitment to make 'gold standard' substance use treatment accessible to all Veterans, VHA announced an initiative supporting nationwide dissemination of CM in 2011 [13,14]. CM is a manualized behavioral intervention that offers incentives (e.g., prize vouchers) for negative drug screens to reinforce abstinence over a time-limited treatment interval. CM has accumulated substantial empirical support over the past 25 years and has been consistently associated with reduced use and improved treatment retention in individuals with CUD [16,27-30], as well as other substance use disorders [16,29,31-33]. Despite these favorable results, however, CM has been underutilized due to insufficient and/or unreliable funding. To address this, VA has specifically adopted a prize-based variant of CM [13,14] which utilizes a lower-cost reinforcement schedule with comparable effectiveness [34] to improve widespread access. Even so, long-term sustainability of CM within the VA remains uncertain and will be bolstered by increased efficiency and effectiveness of CM programming. There are currently two primary considerations with respect to this goal: (1) modifying CM to enhance and sustain benefits and (2) targeting CM in a manner informed by patient needs.

While CM is currently the best-supported treatment for CUD, treatment response is variable [15] and long-term outcomes remain poor [16]. Indeed, a recent meta-analysis of prize-based CM studies identified a medium end-of-treatment effect size but no appreciable benefit at 6 months post-treatment [16]. Low response rates (~40%) have also been reported [35] and current evidence suggests over half of CM responders may achieve similar outcomes in TAU [15,17]. Of note, recent work in Veterans has failed to demonstrate a significant effect of CM relative to TAU for treatment of stimulant use disorders [36], providing an imperative to improve the effectiveness of VA CM programming, specifically. Importantly, previous efforts to improve CM effectiveness have highlighted opportunities to adapt CM treatment parameters in response to individual difference factors. Both increased magnitude [15] and probability [37] of contingent reward, for example, have been demonstrated to increase cocaine abstinence in CM and may be specifically indicated in patients with greater CUD severity [17]. Previous experimental manipulations of CM reflect the intervention's theoretical foundation in operant conditioning – whereby the probability, timing, and magnitude of a reinforcer determines its potential to drive behavior change. These early models of CM conceptualize substance use as a conditioned response to drug-related positive reinforcement (and associated cues) that can be systematically shaped by environmental contingencies. Abstinence-contingent alternative reinforcement introduced by CM therefore works to (1) increase the frequency of abstinence-consistent behaviors and (2) decrease use-related behaviors due to opportunity costs (i.e., loss of alternative reinforcement) associated with drug-taking. Basic tenets of this account are robustly supported within the scientific literature and have framed a preponderance of CM research to date. This alternative reinforcement model of CM may, however, overlook more subtle cognitive components of the intervention that are both necessary to its effectiveness and relevant to optimization and personalization of CM treatment parameters. Consistent

with the alternative reinforcement account, preclinical research supports dramatic devaluation of drug reward when a concrete, non-drug option is made available [38]. Early CM intervention research in humans similarly utilized choice contexts wherein abstinence-contingent alternatives were accessible during use-related decision-making [39]. In practice, however, alternative rewards offered in CM are not immediately available; rather, they occur at some delay (e.g., hours to days after use-related decision-making). Recent critiques have highlighted this aspect of CM, suggesting that the potency of alternative reinforcement in CM depends – not only on the magnitude and probability of future reward – but also on its robust mental representation at the time of decisions to use or abstain [18]. Beyond simple behavioral shaping, CM may therefore be understood to remediate the pathological imbalance between executive and impulsive decision systems underlying CUD by supporting pursuit of delayed (recovery-related) reward over use [19]. Specifically, CM increases the proximity and concreteness of recovery-related reward – factors known to enhance subjective valuation [40]. As these factors have been implicated in CM effectiveness [18], individual differences in future reward valuation provide a promising new opportunity for adaptive intervention delivery. Indeed, poorer outcomes were recently demonstrated in association with steeper devaluation of future reward in low magnitude but not high magnitude reinforcement versions of CM [41]. In sum, existing evidence suggests that alternative reinforcement mechanisms of CM are complimented by processes underlying the representation and valuation of future reward. Accordingly, a novel future-minded decision-making (FMDM) model of CM was recently proposed [18,19] to advance scientific inquiry into, heretofore overlooked, cognitive components of this important intervention. The FMDM model views the overall structure of CM as a scaffold for recovery-oriented goal setting and goal-oriented decision-making. Specifically, by presenting reliable, short-term reward to reinforce abstinence, CM provides frequent opportunities for mental representation of delayed reward and related contingencies. CM can therefore be understood to engage executive working memory processes related to goal maintenance, as well as episodic future thinking – which involves mental simulation of future events. Through these processes, positive outcomes of abstinence can be robustly represented at the time of use-related decision-making and abstinence goals can be more readily accessed to capacitate proactive and reactive control of behavior.

Preliminary Studies

Multimodal Prognostic Assessment of Contingency Management Treatment Outcomes, 2016-present. I received a VISN 4 MIRECC pilot grant to collect preliminary data in support of the current research. This pilot has three objectives: (1) establish feasibility of the proposed design with respect to participant recruitment and retention, (2) optimize parameters of behavioral paradigms for repeated-measures data collection, and (3) evaluate preliminary predictive utility of key FMDM-related measures (ERN, N2, change in delay discounting with inclusion of personally-meaningful future event tags, and working memory function). Data collection was initiated in May, 2017 and concluded in May, 2019; data analysis is ongoing.

Implications/Relevance to Current Project: Our preliminary data demonstrate feasibility of key assessments proposed for use in the current project (i.e., a Parametric Conflict flankers task, modified delay discounting task, and the Brown-Peterson/Auditory Consonant Trigrams test of working memory), as well as successful recruitment and retention of CUD patients. There have been no significant adverse events related to study participation to date.

5.0 * Describe the overall significance of the research in terms of the problem to be studied and potential findings, as well as its relevance to the care of veterans, the VAPHS, and the VHA:

While previous efforts to enhance CM effectiveness have primarily focused on the magnitude and probability of reward, the FMDM model suggests additional promising avenues to enhance benefits and adapt treatment delivery to patient needs. For example, while the lower cost, prize-based version of CM (PBCM) disseminated by VHA necessarily involves uncertain future reward, PBCM has traditionally (and purposefully) utilized tangible reinforcement (i.e., desired material objects displayed within a prize cabinet) rather than monetary incentives to foster concrete representation of future reward. While this "tangible prize" version of CM (TangiblePBCM) has been most widely studied, it is currently used at only ~20% of VA CM sites; rather, the majority of VA CM sites (~80%) use Canteen vouchers to improve convenience and expand prize options. Although matched to traditional TangiblePBCM with respect to reward probability and magnitude, this "voucher prize" version of CM (VoucherPBCM) entails more abstract reward representation that may fail to successfully incentivize abstinence in patients with limited future thinking capacity. Indeed, such patients may fail to convert voucher winnings into tangible prizes – a pattern of behavior that has previously been associated with poorer outcomes in voucher-based programs [42]. Currently, VA sites offering TangiblePBCM primarily do so for practical reasons (e.g., a local VA canteen is not available for voucher redemption) but individual difference factors may also strategically inform selection of TangiblePBCM versus VoucherPBCM on a patient-by-patient or site-to-site basis.

Previous work has demonstrated that adapting CM reinforcement schedules based on patient features has potential to improve overall outcomes while keeping program costs low [17,41]. Specifically, providing higher magnitude reinforcement to patients with a poorer prognosis in CM (e.g., patients who test positive for cocaine at treatment outset or exhibit steeper discounting of future reward) may improve the likelihood of successful treatment response in these individuals. Clinical translation of such findings is, however, impeded by ethical considerations regarding healthcare equity, transparency, and patient preference when the probability and/or magnitude of reward differs between treatment options. Importantly, the FMDM model of CM, highlights new possibilities for personalized treatment adaptation – such as strategically varying the concreteness of future reward – that may be more readily translatable in light of these ethical issues. Identifying patient-level predictors of differential treatment response in TangiblePBCM versus VoucherPBCM, for example, could directly inform CM implementation and may, in fact, improve overall treatment response by matching patients to an appropriate level of future reward abstraction based on FMDM ability. Chronic cocaine users present with varying degrees of impairment across FMDM-related cognitive domains including working memory, attentional control, and decision-making and such deficits have been associated with poor treatment adherence and retention in CUD patients [43,44]. It is plausible that individuals with more pronounced FMDM deficits differentially benefit from TangiblePBCM because concrete delayed reward better supports inhibition of immediate reward preferences [40]. Patients with superior FMDM ability, by contrast, may be better equipped to utilize abstract rewards offered in VoucherPBCM, which may further provide more advanced opportunities to plan and simulate future reward outcomes.

Previous work has already highlighted the potential predictive utility of FMDM-related constructs – identifying improved CM outcomes in individuals with better working memory performance [45] and higher valuation of delayed reward [41]. However, no previous work has studied such predictors in the context of FMDM-informed treatment variants with immediate translational potential within the VA. As

previously indicated, both VoucherPBCM and TangiblePBCM are already utilized in VA substance use clinics but selection of one variant over the other is currently driven by practical considerations alone. The proposed work will determine if a measurement-based approach to implementation of VoucherPBCM versus TangiblePBCM is indicated and will specifically evaluate the potential of FMDM-aligned neural and cognitive markers to guide clinical decision-making. Actionable consequences of the proposed work are summarized in Table 1; additional alternative outcomes (e.g., evidence of differential treatment response in VoucherPBCM versus TangiblePBCM by CUD severity) are not detailed but may also inform delivery of CM within the VA.

Table 1. Relevance of potential empirical observations to PBCM implementation within VA.

	Finding from the Proposed Research	**Recommendation**
Hypothesis	Patients with greater FMDM impairment (as indexed by neurocognitive markers) will demonstrate improved treatment outcomes in TangiblePBCM relative to VoucherPBCM.	TangiblePBCM is recommended for patients with greater FMDM impairment.
	Patients with less FMDM impairment (as indexed by neurocognitive markers) will demonstrate improved treatment outcomes in VoucherPBCM relative to TangiblePBCM.	VoucherPBCM is recommended for patients with less FMDM impairment.
Alternative Outcomes	Treatment outcomes are comparable in TangiblePBCM and VoucherPBCM, regardless of level of FMDM impairment.	TangiblePBCM and VoucherPBCM are equally appropriate for all patients.
	Treatment outcomes are improved in TangiblePBCM relative to VoucherPBCM, regardless of level of FMDM impairment.	TangiblePBCM is recommended for all patients.
	Treatment outcomes are improved in VoucherPBCM relative to TangiblePBCM, regardless of level of FMDM impairment.	VoucherPBCM is recommended for all patients.

Beyond adaptive implementation of existing CM variants, the FMDM model highlights novel pathways to achieve enhanced and sustained benefits of CM. Specifically, the FMDM model suggests CM actively remediates cognitive abilities underlying future-minded decision-making and, by extension, the response rate and long-term outcomes of CM can be improved by strengthening this mechanism of action. For example, while it is already recommended that patients describe desired prize items during each CM session [46], explicit practice with planning and mental simulation of future events has not yet been incorporated into CM protocols. Similarly, working memory training may also serve to complement and extend the benefits of CM [47] and has already been demonstrated to improve valuation of delayed rewards in stimulant users [48], consistent with stronger reward representation. Because FMDM readily generalizes to life contexts outside of treatment, greater emphasis on developing this ensemble of cognitive functions during and after CM may also be key to unlocking long-term benefits of the intervention. However, predictions of the FMDM model regarding neurocognitive recovery during CM remain to be tested. Only one study to date has addressed CM-related changes in neural and cognitive processes – demonstrating recovery of anticipatory reward signaling in thalamus, precuneus, and midbrain in CUDs, consistent with improved delayed reward representation [49]. Establishing recovery of additional FMDM-related cognitive functions (e.g., executive working memory, episodic future

thinking, and inhibitory control) through CM would thus clarify important neural mechanisms of action with strong potential for future development.

In sum, the FMDM model of CM has important implications for personalized treatment delivery and may also reveal novel opportunities to enhance the short- and long-term effectiveness of the intervention. However, key predictions of the model remain to be tested. The current CDA aims to address this knowledge gap by (1) evaluating individual differences in FMDM function as predictors of treatment response in CM variants utilizing concrete (TangiblePBCM) versus abstract (VoucherPBCM) future rewards and (2) examining longitudinal change in neural and cognitive processes underlying putative FMDM-based mechanisms of CM. Ultimately, this line of research aims to improve VA CM programming by clarifying both how and for whom existing versions of PBCM are effective. In particular, understanding the role of FMDM in patient-level outcomes could immediately inform treatment recommendations within VA clinics (wherein both VoucherPBCM and TangiblePBCM are already used). The proposed research may additionally highlight new opportunities to improve CM and aftercare programming through enhanced emphasis on FMDM skill development, maintenance, and generalization. Furthermore, by elucidating neural adaptation within FMDM-related brain networks during CM such mechanisms may be more directly targeted through cognitive training, neurofeedback, or noninvasive brain stimulation in subsequent research.

6.0

Please upload any additional documents:

Name Version

There are no items to display

View: 2.1 Required Reviews

Required Reviews

1.0

Type of Submission:

New study

If this is a 'New Paper Conversion' please include the MIRB Number:

Please upload a letter certifying that you have made no modifications or amendments in converting this research study from paper to electronic:

2.0 * Requested Review Type:

Name

Exempt

Expedited X

Full IRB Review

Not Human Subject Research

3.0

Please check which of the following Service Lines/Departments/Entities will be impacted or used in the conduct of this study

Upload Letter of Support

Clinical Support
Medical Specialty: Medical Service Line LOS (0.01)
Investigational Drug Service
Imaging
Community Based Care
Patient Care Services
Behavioral Health: BH Service Line LOS (0.01)
Primary Care
Surgical Specialty
Critical Care
Clinical Trials Center
Regulatory Coordinator Support Core
Clinical Coordinator
Support Core
Ancillary Support Core
Data Support Core
Research Registry
Registry Number:
Other
If Other, please specify:

View: 2.1.1 Expedited Qualification

REQUEST FOR EXPEDITED REVIEW

Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

AND

Identification of the subjects and/or their responses would not reasonably place them at risk of criminal or civil liability or be damaging to the subject's financial standing, employability, insurability, reputation, or be stigmatizing, or reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are minimal.

1.0

* Please certify that ALL of the following are true:

Case

Research presents no more than MINIMAL RISK to subjects (considering physical, psychological, social, legal and economic risk)

Identification of the subjects and/or their responses WOULD NOT reasonably place them at risk of criminal or civil liability or be damaging to the subject's financial standing, employability, insurability, reputation, or be stigmatizing, OR reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are minimal.

The research is not classified.

The research involves only procedures listed in one or more of the categories listed in Section 2.

2.0 If you check any of the items below, the study is qualified for EXPEDITED review status under federal guidelines.

* Select all that apply:

Description

1. Clinical studies of drugs and medical devices only when condition (a) or (b) is met:

(a) Research on drugs for which an investigational new drug application (21 CFR Part 312) is not required.

(b) Research on medical devices for which an investigational device application (21 CFR 812) is not required OR the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.

2. Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:

(a) From healthy, non-pregnant adults who weigh at least 110 pounds. [not to exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; or

(b) From other adults and children, considering the age, weight and health of the subjects, the collection procedure, the amount of blood to be collected: The amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.

3. Prospective collection of biological specimens for research purposes by non-invasive means. Examples:

(a) hair and nail clippings in a nondisfiguring manner;

(b) deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction;

(c) permanent teeth if routine patient care indicates a need for extraction;

(d) excreta and external secretions (including sweat);

(e) uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax or by applying a dilute citric solution to the tongue;

(f) placenta removed at delivery;

(g) amniotic fluid obtained at the time of rupture of the membrane prior to or during labor;

(h) supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques;

(i) mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings;

(j) sputum collected after saline mist nebulization.

4. Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are used, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical devices are not generally eligible for expedited review, including studies of cleared medical devices for new indications)

5. This research involves materials (data, documents, records, or specimens) that have been collected for any purpose including previous research or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis).

6. This research involves the collection of data from voice, video, digital, or image recordings made for research purposes.

7. This research will be performed on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or will employ a survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.

View: 3 Research Design

Methods & Procedures

1.0

* Does this research study involve any of the following:

Deception

Interview/Focus Groups

Use of Drug, biological, or nutritional (e.g., herbal or dietary) supplement (investigational or FDA approved)?

Use of medical devices

Prospective Analysis of Specimens

Banking of Specimens-Data

Retrospective use of specimens

Audio/Video Recordings or Photographs

Honest Broker or other similar service

None of the Above

View: 3.2 Interview-Focus Groups

Interview-Focus Groups

1.0

* Attach copies of any scripts and/or questions that will be used to guide the interviews/groups:

Name Version

Addiction Severity Index Lite 0.01

CM Qualitative Interview 0.01

MINI for Psychotic Disorders Studies 7.0.2 0.01

Positive-Neutral Future Events Interview Instructions 0.02

Timeline Follow-back Calendar Template: Alcohol 0.01

Timeline Follow-back Calendar Template: Other Drugs 0.01

Timeline Follow-Back Calendar Template: Cocaine 0.01

Timeline Follow-Back Instructions: Baseline 0.01

Timeline Follow-Back Instructions: Check-In/FU 0.01

2.0 * Please describe the Study Team qualifications (for example, special training):

Study interviews will either be directly administered by Dr. Forster or by research staff trained by Dr. Forster. Dr. Forster is a licensed clinical psychologist with extensive training and experience in the administration of structured and semi-structured diagnostic interviews in both research and clinical settings. Dr. Forster has previous experience administering the Structured Clinical Interview for DSM-IV (which requires similar knowledge and skills to administer as the M.I.N.I. 7.0.2), Addiction Severity Index, and Timeline Follow-Back procedure. In addition, instructions for the Positive-Neutral Future Events Interview were developed by Dr. Forster based on experience soliciting similar information through unscripted interviews during her pilot project (Pro1787). A series of qualitative interview questions were also developed by Dr. Forster based on her experiences working with Veterans in Contingency Management in both clinical and research contexts.

View: 3.4 Use of Medical Devices

Medical Devices

1.0

* Specify all devices used on this study:

Device Name Manufacturer Use of Device IDE Number(if Applicable) Device Brochure Description of Use Risk Level Determined by Sponsor

acti32Champ EEG Acquisition System Brain Products GmbH Investigational Device Not Yet Approved for use actiCHamp Manual(0.01) This is a nonmedical device that will be used for the acquisition of electroencephalography (EEG) data in accordance with manufacturer operating standards. This device is non-invasive and will only be used to monitor naturally-occurring biological signals and processes in vivo. The actiCHamp is intended to be used for research applications only and is not sold, designed or intended to be used as medical devices as defined in EU Directive 93/42/EEC, nor is it intended to be used for other medical applications such as diagnosis or treatment of disease. The actiCHamp hardware has been tested and certified as per the relevant EMC and electrical safety standards. A non-medical CE certificate is available on request. This equipment was reviewed and approved for purchase by the VAPHS Bio Medical Review committee on 5/9/2019. Non-Significant Risk

GT3XP-BTLE 4GB Activity Monitor Actigraph, LLC FDA Approved Device used in approved manner n/a Actigraph Brochure(0.01) GOLDSTEIN SUBSTUDY ONLY: This device will be used in accordance with manufacturer instructions. The device tracks physical activity, sleep, and heartrate data (logged from a linked Polar H7 device). ActiGraph activity monitors are FDA 510(k) cleared and ActiGraph is ISO-13485:2016 certified. Non-Significant Risk

ISCAN model RK406 Infra-red Pupillometer ISCAN FDA Approved Device used in approved manner n/a ISCAN Website(0.01) This is a Class I medical device that will be used in an approved manner to monitor eye movement, pupil dimensions, and blinks during the EEG procedure. This device is non-invasive and will only be used to monitor naturally-occurring biological signals and processes in vivo. Non-Significant Risk

Polar H7 Polar FDA Approved Device used in approved manner n/a Polar H7 Info Sheet(0.01) GOLDSTEIN SUBSTUDY ONLY: This device will be worn around the chest to remotely measure heart rate. These data are transmitted via Bluetooth to the linked ActiGraph device for storage. Polar fitness monitors have been provided FDA 510(k) clearance. The Polar H7 is currently marketed as a commercial device and will not be used to diagnose, treat, or prevent a medical condition. Non-Significant Risk

2.0 * Describe your plan for storage and control of devices:

The BrainVision acti32Champ EEG acquisition system and ISCAN Pupillometer will be stored in the VAPHS Biometrics Laboratory in consultation with Dr. Steinhauer - a leading expert in electrophysiology and pupillometry. Equipment will be routinely tested and data monitored in order to ensure safe and effective operation.

Activity and heart rate monitors will be stored in accordance with manufacturer instructions and will be cleaned and sterilized between each use.

View: 3.5 Prospective Analysis of Specimens

Prospective Analysis of Specimens

1.0 * Please provide a description of samples to be collected:

Samples Collected in the Context of Baseline, Check-In, and Follow-Up Study Visits (*No Direct Identifiers*):

Urine and/or oral saliva specimens will be collected/tested at baseline using commercially-available drug test kits and specimen containers. We will also collect and test urine and/or oral saliva at the time of the follow-up EEG assessment. In addition, urine specimens may also be collected and tested using commercially-available drug test kits at check-in appointments if the participant is not actively involved in CM and/or has missed recent CM visits. However, it is noted that collection of such supplemental urine specimens at check-in timepoints would not apply if (1) lab-based urinalysis for substance use has recently been completed for clinical or research purposes, (2) the participant refuses, or (3) the participant is not available or able to provide a specimen. All urine and oral saliva specimens collected for testing with commercially-available drug test kits in the context of these described research activities will be marked with indirect identifiers only and will be disposed of immediately after testing.

Samples Collected in the Context of Treatment (CM; *Direct Identifiers*):

During the 12 week treatment interval, patients will be subject to routine urinalysis (twice weekly). Urine specimens will be collected (and may be witnessed, if necessary) by nursing staff at the Center for Treatment of Addictive Disorders (CTAD) or research staff at the Research Office Building and tested for cocaine (and possibly other substances) by the CM therapist using a point-of-care diptest in order to provide the patient with immediate results for the purpose of determining CM prize draws. Confirmatory urinalysis will subsequently be conducted to verify point-of-care results. Urine specimens will therefore be forwarded to VAPHS laboratory staff for processing. For this reason, urine specimens collected in the routine clinical course of CM will be marked with direct identifiers prior to submission to the lab. However, it is noted that all urine collection/testing procedures to be conducted within the context of CM parallel those already used in routine clinical (i.e., non-research) administration of CM and other substance use treatment programming at VAPHS. It is additionally noted that participants may always decline to provide observed urines for lab-based processing and may alternately elect to provide urine specimens (not marked with direct identifiers) for kit-based testing by research personnel, as described above.

2.0 * Please describe the tests or analyses to be performed on the study specimens:

Both oral saliva and urine specimens will be tested with commercially-available test kits that automatically screen for specific substances of abuse and provide results within seconds to minutes. Commercially-available test kits generally involve exposure of specimens to a specially designed test card that visually changes to register the result (similar to a drug store pregnancy test). A subset of urine specimens (i.e., urines collected for treatment purposes and marked with direct identifiers) will additionally be subject to confirmatory urinalysis at the VAPHS onsite laboratory by laboratory staff. Details of laboratory-based testing can be provided upon request.

3.0

* Sample Collection Method:

Samples to be obtained will be limited to amounts routinely collected during a clinical procedure. This includes samples normally taken by Pathology for diagnostic purposes.

Samples will consist of additional material taken during a clinical procedure

Samples will be obtained via a separate collection procedure done solely for the purposes of this research

4.0

* Please indicate how the specimens will be identified at the time they are forwarded for use in this research:

DIRECT IDENTIFERS will be included with the specimens

INDIRECT IDENTIFIERS (codes,links) will be noted on specimens

If multiple selections have been made, please describe why:

As described above, specimens collected in the context of routine CM care during the 12 week treatment interval will be identified with direct identifiers because these samples will be subject to lab-based processing and urinalysis. With respect to these specimens, the "Samples to be obtained will be limited to amounts routinely collected during a clinical procedure," and will be collected in the context of the patient's routine clinical care.

Specimens collected for the purpose of objectively verifying recent abstinence for research purposes will not be marked with direct identifiers and will be tested and immediately disposed of by research staff. While these samples will also "be limited to amounts routinely collected during a clinical procedure" they will be collected solely for the purposes of research. We will therefore take additional steps to protect patient confidentiality with respect to these samples: (1) eliminating direct patient identifiers from the specimen collection procedure, (2) immediately disposing of samples following testing, and (3) utilizing only indirect identifiers (subject ID code) when recording test results.

5.0 * Will the analysis to be done on the samples possibly result in any genetic information related to the subject's (or his/her relatives') health or susceptibility to a disease or condition currently or in the future?

Yes **No**

If yes will patients have access to this information?

Yes No

6.0

* Will the analysis to be done on the samples involve whole genome sequencing?

Yes **No**

If Yes, for research compliant with the 2018 Requirements, if the research involves whole genome sequencing (sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen), there must be a statement indicating that the research will or might include whole genome sequencing in the consent.

7.0 * Please list where processing of these specimens will occur:

Collection/processing of specimens will occur in clinical areas of Buildings 29 and 30. Specifically, samples collected for research purposes in Building 30 will be collected/processed in the following locations: GA124, GA112, GA110, and Building 30 Lobby restrooms. These locations include a patient restroom in the clinical trials center on the group floor of the Research Office Building, as well as two exam rooms available on the ground floor of the Research Office Building. Samples collected as part of clinical care through the Center for Treatment of Addictive Disorders (CTAD) will either be collected by nursing staff in one of several patient restrooms used for clinical urine collection in Building 29 or by research staff in Building 30 locations listed above. For patients assigned to Contingency Management, these samples will then be subject to point-of-care testing in a designated clinical area/treatment room within Building 29 or a comparable space in Building 30. Samples collected during the treatment interval will typically be marked with direct identifiers and forwarded to the onsite laboratory facility for additional processing and confirmatory drug-alcohol urinalysis.

Plan for Destruction/Disposal of Specimens. Urine and oral saliva specimens collected for research purposes (indirect identifiers only) will be disposed of by study personnel immediately after testing. Following use, oral saliva test kits will be disposed of in red, biomedical waste containers. Similarly, used urine dip tests and urine specimen containers will be disposed of in red, biomedical waster containers after any remaining urine has been poured into a toilet and flushed down the drain. Urine specimens collected in the context of clinical care (direct identifiers) will be disposed of by VAPHS laboratory personnel after processing, using standard procedures approved by the medical facility for the destruction of urine specimens and specimen containers with direct patient identifiers.

View: 4 Research study methods

Research Study Methods

Describe all study related procedures following enrollment of a subject in this study.

Please see Section 6 for where the study team defines when a subject will be considered enrolled in the study.

1.0

* Research Procedures/Interventions:

Informed Consent and Screening Visit. The initial study visit will involve review of the informed consent document and discussion of any participation-related concerns. During the informed consent process, participants will be informed of drug and alcohol testing conducted at the time of the Baseline Assessment and that a minimum of 72 hours of abstinence from cocaine and other illicit substances is required prior to participation in baseline testing. After written informed consent has been obtained, the participant will be enrolled in the study. A brief cognitive screening tool (the Saint Louis University Mental Status (SLUMS) or Mini Montreal Cognitive Assessment (MoCA)) will be administered to determine eligibility for participation in all subsequent study procedures. However, it is noted that we will routinely conduct cognitive screening via the Mini MoCA as part of our initial (typically telephone-based) eligibility assessment in order to reduce burden on participants who are deemed ineligible based on this criterion. In this way, individuals who will not meet our full eligibility criteria will be more efficiently screened out with less time invested. For this reason, cognitive screening will only occur at the Consent and Screening Visit if not already completed. Evaluation of psychiatric and substance use history will follow for all individuals who pass cognitive screening. Participants may also be asked to complete a Demographic Information form and Contact Information form during this visit and may additionally be provided with self-report questionnaires, which they may choose to complete in the time between the Screening Visit and Baseline Assessment. It is further noted that this session may be remotely conducted to reduce burden/risks to participants. In such cases, assessments will be completed via telephone of video call (using locally approved technologies) and, when necessary, forms will be transmitted via mail, email, or warm handoff (e.g., during a clinical interaction with one of the Veteran's providers).

Diagnostic Interviews and Neuropsychological Screening. The investigator or a trained research assistant will administer the Mini International Neuropsychiatric Interview (MINI) 7.0.2 (specifically, the version for studies including patients with psychotic illnesses), Saint Louis University Mental Status (SLUMS) or Mini Montreal Cognitive Assessment (Mini MoCA) exam, and Addiction Severity Index-Lite (ASI-Lite) to all study participants. The investigator has extensive experience administering the SCID - a semi-structured interview similar to the MINI - in research and clinical contexts and has received training on this instrument under the direction of one of the authors (Michael First, MD). The investigator also has sufficient experience with the SLUMS and ASI from previous research and clinical training. The MINI will be used to identify comorbid psychiatric and substance use diagnoses, as well as CUD severity. The SLUMS or Mini MoCA will be administered to screen for moderate-to-severe cognitive impairment. Previously undiagnosed conditions identified through administration of the MINI or SLUMS/MoCA that may be relevant to the Veteran's ongoing care will be shared with the Veteran's mental health treatment coordinator. The participant will be made aware of this policy during the informed consent process. Participants determined to be eligible following participation in diagnostic interview and neuropsychological screening procedures will be scheduled for a Baseline Assessment. It is possible that the Informed Consent and Screening Visit and the Baseline Testing Visit could occur on the same day if scheduling these visits for separate days would be problematic for the participant.

▪ MINI International Neuropsychiatric Interview for Psychotic Disorders Studies (Version 7.0.2): The MINI is a semi-structured clinical interview based on DSM-5 diagnostic criteria. Module J (Substance Use Disorders) will always be administered in full. A screening tool will be used to identify symptoms relevant to other diagnostic categories and additional modules will be administered, as needed, to limit the total time burden. Veterans identified as having additional, immediate assessment or treatment

needs will be escorted to the VAPHS Behavioral Health walk-in clinic or Emergency Department (if determined to pose an imminent risk of harm to self or others). Diagnostic evaluation using the MINI will enable determination of CUD severity and effective characterization of psychiatric and substance use comorbidities.

▪ Addiction Severity Index-Lite (ASI-Lite): The ASI-Lite is a semi-structured interview used to quantify problem severity related to alcohol and drug use, as well as functioning in five domains impacted by addictive disorders: medical status, legal status, psychiatric status, family/social status, and employment/financial support. The ASI is commonly used to quantify overall severity of addictive disorders – a factor which must be considered when evaluating individual differences in substance use treatment response.

▪ Cognitive Screening via One of the Following Tools (if not conducted during initial eligibility assessment):

▪ Saint Louis University Mental Status (SLUMS): The SLUMS is a brief cognitive screening tool, used to identify impairment across eight domains: working memory, concentration, attention, orientation, semantic fluency, visuospatial ability, executive function, and short-term recall. A cutoff of 20 is suggested to identify dementia and serious cognitive impairment; individuals scoring ≤20 will be excluded from further participation.

▪ Mini Montreal Cognitive Assessment (MoCA): The mini version of the MoCA is brief cognitive screening tool that can be used as an alternative to the SLUMS for remotely conducted (i.e., via telephone or video call-based) cognitive screening. A cutoff of 10 is suggested to identify dementia and serious cognitive impairment; individuals scoring ≤10 will be excluded from further participation.

Baseline Assessment. The Baseline Assessment session for CM veterans and healthy controls could include the following components:

Substance Use Assessment: Recent substance use will be evaluated through self-report and objective testing.

▪ Breathalyzer and Oral Saliva Drug Testing: Participants will be required to pass breathalyzer (BAC = 0.000%), as well as urine and/or oral saliva drug screens (negative for all common illicit substances, excluding marijuana) in order to participate in baseline testing. Such testing is necessary to establish that participants are not acutely intoxicated at the time of EEG and cognitive-behavioral assessments, which may compromise the validity and reliability of these measures. We will offer oral saliva testing as an option because this method has an earlier and more proximal detection window than urine-based testing (sensitive to use immediately prior to testing and during the preceding 72 hours). Consequently, it will be possible to include CUD participants with relatively short durations of cocaine abstinence prior to baseline testing. Participants will be informed of drug and alcohol testing procedures at the screening visit and asked to abstain from drug use for 72 hours prior to testing. While this requirement will necessarily exclude individuals who are unable to abstain for 72 hours, such individuals would generally not be recommended for CM programming (VA CM implementation consultants suggest 3-4 days of demonstrated abstinence prior to initiating a CM referral). Consequently, this requirement should not prevent us from achieving a representative sample of cocaine users for whom CM is indicated. Due to

the requirement that participants pass initial drug-alcohol screening, individuals with anticipated or observed difficulty achieving initial abstinence may elect to schedule one or more optional pre-CM testing sessions with study personnel in preparation for the Baseline session.

▪Timeline Follow-Back (TLFB) Procedure: During the timeline follow-back, participants will be asked to describe drug and alcohol use during the past month, including type, frequency, and quantity. Typical patterns of pre-treatment drug and alcohol use may also be evaluated if a recent change in use has preceded the testing session (for example, patient completed residential treatment during the past month).

EEG Procedure: Participants will complete two computerized behavioral tasks while EEG is recorded from the surface of the scalp using a commercially-available EEG recording system. A baseline (resting) acquisition may also precede task-related data acquisition, as is typical for EEG recording procedures.

▪ Concrete-Abstract Incentive Delay Task: In order to evaluate differences in alpha suppression during anticipation of concrete/tangible versus abstract/monetary reward, EEG will be recorded while participants perform a modified Monetary Incentive Delay task with voucher- and tangible-prize reward cues. Previous work has demonstrated that reward cues associated with more concrete or primary rewards result in greater alpha suppression during anticipation [50], as well greater recruitment of brain areas associated with self-referential and prospective processing [51] when compared with monetary reward cues. A paradigm previously used to examine anticipatory brain responses to monetary versus food rewards [51] will be adapted for use with voucher and tangible prize rewards. Trials will begin with a cue indicating reward magnitude (i.e., no reward, low reward, high reward), followed by a delay and target stimulus (requiring a manual response). Another delay will precede presentation of feedback based on response accuracy and reward magnitude. Consistent with previous work [51], reward feedback will consist of images depicting either monetary prizes (vouchers) or prize baskets with tangible items (e.g. snacks, clothing, household goods). Participants will be informed that they will not receive total prize winnings but that a percentage of total winnings will be awarded following the task (a strategy the PI has successfully used in previous work); the value of this prize bonus will generally be between $15-25. Participants may additionally choose to have this bonus paid out as part of their standard participant compensation for the session or select one or more prize cabinet prizes of matching value.

▪ Parametric Conflict Flankers Task: As previously described, FMDM requires robust goal representation to inform effective proactive and reactive modulation of cognitive control. In order to assess control-related processes, a modified Eriksen Flankers paradigm will be used to measure transient theta frequency synchronization of brain signals recorded at ACC and lPFC electrode sites, as well as ERN and conflict N2 components of response- and stimulus-locked event-related potentials, respectively. In this modified version of the task, trial-to-trial response conflict will be parametrically manipulated through different levels of flanker-target incongruity (i.e., Congruent, Incongruent-Low, Incongruent-Medium, and Incongruent-High). The Parametric Conflict Flanker task has previously been validated in healthy controls [52] and in individuals with nicotine use disorder [53]. The deadline for response production will be adjusted on a subject-by-subject basis to ensure an appropriate number of erroneous responses and to establish a similar level of task difficulty across participants and over time.

Cognitive-Behavioral Testing: Additional FMDM constructs will be measured using cognitive tasks.

▪ Personalized Delay Discounting Task: Participants will be interviewed about upcoming positive and neutral life events (e.g., birthdays, holidays, vacations), occurring at latencies ranging from one week to one year from the testing date. Events will be rated with respect to personal relevance, valence, and arousal and a subset of events with similar ratings will be selected for use in a personalized version of the delay discounting task. Following previously described procedures [54], participants will complete a series of delay discounting trials with and without inclusion of event tags referencing personally-meaningful future events from the interview. Blocked presentation of trials in each condition allows for characterization of standard delay discounting behavior (i.e., without event tags) as well as discounting in the context of episodic future thinking (with event tags). The difference in delay discounting slopes estimated for each condition (i.e., Δ ln(k)) will be used as a measure of future-minded decision-making. Specifically, greater reduction in discounting slope with inclusion of event tags signifies greater engagement of episodic future thinking, thus increasing valuation of future reward. Upon completion of the task, participants will also be asked to rate the vividness and frequency of spontaneously-evoked mental imagery associated with each event tag.

▪ Modified Brown-Peterson/Auditory Consonant Trigrams Test: A version of the Brown-Peterson/Auditory Consonant Trigrams test will be used to assess executive working memory. In this test, participants will be required to maintain letter sequences in working memory while performing a distractor task (serial subtraction by threes). Participants will either be asked to immediately recall letters or recall them following a delay. On delay trials, participants will be provided with a letter sequence and starting number and will count backwards by three, out loud, for the duration of the delay period; the letter sequence will then be recalled. This complex-span test is used to index maintenance and decay of working memory contents of direct relevance to the strength of goal maintenance. Of note, low scores on this task have previously been associated with increased externalizing psychopathology and discounting of future reward [55] but the paradigm has not yet been studied in CUDs receiving CM.

Self-report Questionnaires: Participants will also complete measures of craving (Drug Craving Questionnaire, Alcohol Craving Questionnaire) [56], sensation seeking (Sensation Seeking Scale) [57], avoidance and inflexibility in response to cocaine triggers (Avoidance and Inflexibility Scale) [58], motivation for change (Stages of Change Readiness and Treatment Eagerness Scale (SOCRATES)) [59], previous cocaine relapse experiences (Time to Relapse Questinnaire) [60], sensitivity to reward and punishment (Sensitivity to Punishment/Sensitivity to Reward Questionnaire-20 (SPSRQ-20)) [61], subjective experience of retrospective and prospective memory proficiency (Prospective-Retrospective Memory Questionnaire) [62], self efficacy (Drug Taking Confidence Questionnaire) [63], future mindednesss (Consideration of Future Consequences Scale) [64], nicotine dependence (Fagerstrom Test for Nicotine Dependence) [65], and adverse experiences in childhood (Adverse Childhood Experiences questionnaire) [66]. These instruments were chosen to measure clinically-relevant factors in substance use treatment (e.g., motivation, craving, and impulsivity), as well as factors previously associated with CM treatment outcomes specifically (avoidance-inflexibility) [58]. In order to assess the motivational salience of potential CM incentives, participants will also be asked to complete a Prize Preference and Interest Survey (currently in development, awaiting information on product inventory from VA Canteen Services), wherein interest in/preference for potential tangible and voucher prizes will be rated on a likert-type scale. For participants assigned to TangiblePBCM, this information may also be used to populate the prize cabinet with preferred items.

For healthy participants, participation in activity/heartrate monitoring activities will be described in the primary study consent form and participants may engage in these activities without additionally providing consent under Substudy 2.

Randomization. Following baseline testing, patient participants will be randomized into TangiblePBCM (n = 70) and VoucherPBCM (n = 70) conditions. We will stratify on one or more of the following variables: age, involvement in medication-assisted treatment for opioid use disorder (yes/no), working memory score from modified Brown-Peterson test (< or ≥ Veteran-specific norm), and current diagnosis of bipolar or psychotic illness (yes/no). A minimization approach may additionally be employed in order to allow for stratification on an expanded set of potentially-relevant clinical and demographic factors. Working memory ability was identified as a potential focus of stratification because it is expected to relate to other FMDM constructs of interest and Veteran-specific norms are available for the modified Brown-Peterson test [67]. Participants will be informed of PBCM treatment assignment during scheduling of the initial CM treatment appointment. Participants previously assigned to a TAU only condition will continue to be followed for check-in and follow-up procedures if agreeable to doing so. To maximize options for future data analysis, this may apply to individuals previously assigned to TAU who elect to begin standard PBCM through CTAD rather than continuing in the TAU only treatment condition as part of the study.

Treatment. All participants will receive treatment-as-usual during the 12-week treatment interval, which will entail recommended participation in at least two outpatient group and/or individual psychotherapy encounters through CTAD per week; participants will additionally continue pharmacotherapy for substance use and/or other mental health conditions, if applicable For participants assigned to either Prize-based Contingency Management (PBCM) condition, PBCM will be used and implemented in accordance with the VA protocol for CM, as well as guidance on PBCM, more generally. PBCM involves one-on-one sessions with a provider, during which a urine specimen provided by the patient is tested for cocaine using a point-of-care dip-test. Results of point-of-care testing are then shared with the patient and negative results are reinforced with draws from a fish bowl containing 500 paper slips, 250 of which award small, large, or jumbo prizes (remaining slips deliver words of encouragement). Patients are reinforced with a single prize draw for their first negative specimen; an additional prize draw is added for each consecutive negative result (up to 8 prize draws per session). Abstinence-contingent prize draws are reset to one upon either a positive test result or missed appointment. The proposed work will systematically evaluate two variants of PBCM used within the VA (detailed below) which will be administered twice weekly during 15-20 minute sessions over a 12 week period. The probability of each reward magnitude will be the same in both treatment conditions. Specifically, 41.8% of paper slips will award a small prize, 8% will award a large prize, and 0.2% will award a jumbo prize. During the active treatment period, CM treatment data (i.e., attendance, urinalysis results, prize outcomes) will be logged by the CM provider, and may also be followed through chart review. Participants will additionally be asked to provide regular updates regarding any changes in their housing status or medications (including changes in dosing schedule and/or clinic privileges for patients in medication-assisted treatment) and participation in non-VA substance use treatment (e.g., 12-step meetings in the community). Under unusual circumstances in which a Veteran's prolonged absence from in-person treatment is unavoidable (e.g., due to illness or travel) one or more CM sessions may be conducted via VVC using oral fluid testing (i.e., methods already reviewed and approved under Substudy 1).

▪ TangiblePBCM: For participants assigned to TangiblePBCM, prize draws resulting in one or more small, large, or jumbo wins will result in access to a prize cabinet stocked with small (approximately $0.75-$1.25 in value), medium (approximately $3-$5 in value), large (approximately $20-25 in value), and jumbo (approximately $75-$100in value) incentive items. Medium incentive items are included for selection in the event that a patient draws several small prize slips on the same day and are considered equivalent to 4-5 small prizes. Selection of specific prize items will be informed by patient preference and items will be restocked regularly. The prize cabinet will be open during TangiblePBCM sessions such that prize items are readily visible. Selection of prizes, maintenance of the prize cabinet, and policies regarding prize redemption will follow guidance on administration of TangiblePBCM within the context of research protocols [68].

▪ VoucherPBCM: For participants assigned to VoucherPBCM, prize draws resulting in one or more small, large, or jumbo wins will be reinforced with VA Canteen vouchers in the specified incentive range. Participants in this condition may additionally be asked to provide information on voucher redemption using a self-report or clinician/researcher-administered CM Voucher Survey.

Weekly Check-In Appointments (12 Weeks). Participant outcomes (outpatient treatment engagement, % cocaine-negative urines, self-reported days of use) will be followed throughout the 12 week treatment interval; during this period the timeline follow-back procedure will be administered by phone or in-person on an approximately weekly basis. During the treatment interval, the timeline follow-back procedure will always be administered such that the beginning of the assessment interview corresponds with the last occurrence of the timeline follow-back procedure. In this way we will endeavor to collect self-reported substance use data for the full 12 week treatment interval. This effectively means that one or more missed check-in appointments may be administered at the time of the next check-in attended, if needed. Outpatient substance use treatment engagement and urinalysis results will be monitored through review of participant medical records. Participants will additionally be asked to provide regular updates regarding any changes in their housing status or medications (including changes in dosing schedule and/or clinic privileges for patients in medication-assisted treatment) and participation in non-VA substance use treatment (e.g., 12-step meetings in the community). For CM participants, this information may be gathered, in part or in full, during 1:1 CM treatment appointments. This information will, however, also be assessed during check-in appointments to ensure that relevant information is reliably tracked for all participants, regardless of current participation in CM sessions (see Supplemental Check-in Questions uploaded under Section 3.2).

Follow-up Visit: A subset of procedures from the Screening/Baseline Assessment will be repeated at the conclusion of the 12 week treatment interval for all participants. Procedures will generally involve repetition of the EEG procedure, re-administration of cognitive/cognitive-behavioral testing, and re-administration of one or more self-report questionnaire measures. The timeline follow-back procedure will generally also be completed again at the time of the follow-up visit and specific items from the Addiction Severity Index Lite may also be re-administered. To optimize test-retest reliability of the Personalized Delay Discounting task (if applicable), we will attempt to identify a new set of personally-relevant future event tags with similar valence, salience, and arousal to those utilized at Baseline Assessment through repetition of the Positive-Neutral Future Events interview at the time of the Follow-up Visit. A-B variants of cognitive/cognitive-behavioral tests may also be employed as needed. It is noted that, in some cases, the follow-up visit may occur earlier or later than 12 weeks following treatment initiation. Some flexibility in the timing of the follow-up session may be necessary in order to

maximize our opportunities to collect post-treatment data on as many participants as possible. It is, for example, possible that a participant might conclude treatment earlier than 12 weeks due to returning to work or moving out of the area. In such cases, we would invite the participant to complete the follow-up session early. Similarly, delays in scheduling of the follow-up session may also occur for a variety of reasons. Provided that the participant is still willing to complete the follow-up session, this session may therefore also be scheduled to occur more than 12 weeks from the start of treatment. For healthy controls, a follow-up visit will also be conducted after the initial session, at a delay similar to that achieved within the patient sample. This session may include repetition of other measures conducted at baseline, which can include the repetition of the EEG procedure, cognitive-behavioral testing, and/or self-report questionnaires.

Monthly Check-In Appointments (24 Weeks). CM-assigned participants will engage in research visits on an approximately monthly basis for 6 months following the 12 week treatment period. Timeline follow-back data will be the primary outcome measure and will be collected by phone or in-person. We will also continue to monitor outpatient substance use treatment engagement and urinalysis results through review of participant medical records during this time period. During the post-treatment follow-up interval, the timeline follow-back procedure will always be administered such that the beginning of the assessment interview corresponds with the last occurrence of the timeline follow-back procedure. In this way we will endeavor to collect self-reported substance use data for the full 6 month post-treatment interval. This effectively means that one or more missed check-in appointments may be administered at the time of the next check-in attended, if needed. Healthy controls will not participate in Check-in Visits.

If necessary, longer research visits (e.g., Screening/Consent, Baseline, Follow-up may occur over one or more sessions in order to support complete data collection.

Unexpected Findings: While EEG procedures will be conducted for research purposes only, it is possible that abnormal patterns of brain activity could be detected during the procedure. While we do not anticipate such incidental findings due to the nature of the EEG procedure and equipment to be utilized, participants will be informed that such findings are possible during the consent process, as well as of our procedure for handling such findings should they be detected. Specifically, participants will be informed that we will inform their primary care physician of any incidental findings from the EEG procedure in order to ensure that appropriate clinical follow-up can be initiated. It is also possible that we might identify new information about a participant's current mental health as a consequence of clinical interviews conducted in the context of the study. For example, it is possible that we will identify that a participant meets criteria for a mental health condition that has not previously been documented in his/her medical record. Participants will also be informed of this possibility during the consent process and we will ask to share any such findings with the participant's mental health treatment coordinator. Finally, it is possible that a participant will have a breathalyzer test result that places him/her above the legal limit to operate a motor vehicle (BAC $\geq$ 0.08). In such cases, we will repeat the breathalyzer test to confirm the result and, if the second test result confirms a BAC $\geq$ 0.08 we will contact the VA police with the participant's name and location. The VA police will then respond according to their procedure for handling intoxicated patients who are at risk of driving. Participants will also be informed of this policy during the informed consent process and will have an opportunity to ask questions. Participants will also have the opportunity to decline participation if they do not agree to any policies regarding the handling of incidental or unexpected findings.

Appointment Reminders: Phone outreach will generally be conducted prior to the Screening Visit, Baseline Assessment, and Follow-up (Post-Treatment) Visit in order to remind participants of these upcoming appointments and, if necessary, provide additional information (e.g., instructions for preparing for the appointment, directions to the Research Office Building). Participants may also be provided with a written appointment reminder (see Section 8). Weekly check-ins will generally be conducted during scheduled CM treatment visits but may also be conducted by phone or during a research visit outside the context of a CM treatment session (for example, this will be the case for participants assigned to treatment-as-usual). Phone calls may therefore also be conducted, as necessary, to schedule and/or remind participants of upcoming check-ins. Monthly check-ins will generally be conducted by phone; however, a reminder phone call may also be made prior to a scheduled monthly phone check-in if needed or requested by the participant.

Retention Procedures: Due to the nature of our study population (treatment-seeking substance users) it may be necessary to reschedule initial study appointments (e.g., Screening Visit, Baseline Assessment) due to No Shows, recent substance use, or other factors. For example, it is not uncommon that motivation to engage with substance use treatment will fluctuate and patients may, for example, cancel or postpone initial appointments for this reason. In order to capture a representative sample of treatment-seeking substance users we will make efforts to reschedule initial study appointments that have been cancelled or missed as long as the following conditions are met: (1) the participant continues to express strong interest in study participation and (2) the participant continues to meet general eligibility criteria for the study. With respect to the latter condition, a previously eligible participant may, for example, become ineligible prior to completing initial study appointments if he/she elects to begin Contingency Management treatment prior to completing these appointments. However, as stated later in this protocol, eligibility will be assessed prior to enrollment and there may be some cases in which the duration of abstinence exceeds that stated in our criteria such that an interested participant can be rescheduled for a missed initial research appointment without encouraging resumed cocaine use in order to continue meeting eligibility criteria. Because participants may only begin treatment offered through the study after completing the Screening Visit and Baseline Assessment, individuals will be reminded that they can elect to pursue Contingency Management treatment outside the context of the study if they wish to begin treatment at an earlier timepoint than what might be possible through the study. It may also be necessary to re-evaluate eligibility and repeat screening/consent (and potentially baseline testing) procedures for individuals who have previously engaged with the study but have not progressed to the point of randomization in the past. For example, this may apply to individuals whose progress through the study was interrupted by the COVID-19 pandemic. Given the longitudinal nature of the current project, we will also make every reasonable effort to follow-up with participants who have been randomized into one of the two study treatment conditions. Importantly, participants assigned to Contingency Management will have access to a 12-week course of treatment, regardless of attendance during treatment (or continued participation in the study). Consequently, unless a participant has voluntarily withdrawn (or been withdrawn) from treatment, we will make an effort to schedule Contingency Management appointments throughout the 12 week treatment period. This may involve up to three outreach attempts (phone and/or letter) after a missed appointment. We will follow a similar protocol for missed research check-ins, as well as for the Follow-Up Visit. For missed check-in appointments, we will typically make up to five outreach attempts (phone and/or letter). However, because our study population may have inconsistent telephone service, an additional five outreach attempts may be made, as needed (for example, in cases in which a participant's mobile phone service

has been temporarily disabled). This outreach protocol will also apply to scheduling and/rescheduling of the Follow-Up Visit. We will additionally ask participants to provide an optional alternative contact for research-related communications. Optional alternative contact information may be used to convey HIPAA-compliant messages to participants or to request updated contact information for a participant who has been difficult to contact through contact information listed in his/her chart. Participants may also elect to update or rescind alternative contact information at any time. Participants will be reminded that they may withdraw from the study at any time in retention-related communications (for example, see letters included under Section 8). We will otherwise continue to attempt weekly or monthly check-ins (depending on condition assignment and study phase) on a weekly or monthly basis, respectively, for all actively enrolled participants. For participants who do not respond to the previously described outreach effort and are approaching the end of the study interval, we will transmit a final outreach letter to the participant that will provide study contact information, instructions for withdrawal from the study, as well as the date upon which study participation will automatically terminate. For participants assigned to Treatment-as-Usual, this date will be 30 days after the end of the 12-week treatment interval and for participants assigned to one of the two Contingency Management conditions, this date will be 210 days from the end of the 12-week treatment interval (i.e., 30 days after the 6-month post-treatment timepoint).

Chart Abstraction Procedures: Information in participant electronic health records will be reviewed and data from CPRS may be added to study records at several points during the study. Prior to providing written informed consent, prospective participants undergoing telephone screening will be asked to verbally consent to review of their CPRS records by study personnel. During screening procedures (and following either verbal (by phone) or written (in person) consent), information relevant to participant eligibility will be reviewed and documented. Eligible participants who enroll in the study will also be subject to additional chart abstraction procedures throughout the course of the study. Chart abstraction will generally occur on an approximately weekly basis during the 12 week treatment interval and will primarily involve documentation of outpatient substance use/behavioral health treatment engagement, missed and cancelled substance use/behavioral health appointments, missed doses of medication-assisted treatment (if applicable), lab-based drug-alcohol urinalysis results, changes in medications, changes to housing or legal status, and/or any other relevant changes to psychiatric of medical status. Data from Contingency Management sessions may also be reviewed for consistency with study tracking logs. In addition, data on previous courses of Contingency Management participants may additionally be abstracted for those with prior Contingency Management treatment experience. Following the 12 week treatment interval, chart abstraction procedures will continue for participants assigned to one of the two Contingency Management treatment conditions but will occur on an approximately monthly basis. Examples of forms used for Chart Abstraction thought the Dacima Clinical Suite are included under Section 15 (Miscellaneous Documents). Following consent to the study, data on engagement with CM treatment, not delivered through the study, may also be derived from review of the patient's chart.

Use of Meal Tickets: Participants will be eligible to receive a same-day meal ticket if scheduled for >3 hours of testing during any given visit. In order to ensure comparable prize options for participants assigned to VoucherPBCM and TangiblePBCM, a meal ticket option will also be made available in the CM Prize Cabinet.

Use of Bus Tickets: Need-based travel assistance will be made available to all participants in the form of single use bus tickets.

Please upload a table of procedures if applicable.

The study procedures table must be completed for:

- All Greater than Minimal Risk (GTM) studies; and

- All Minimal Risk studies that use Standard of Care or Usual Care/Interventions.

Name Modified Date

Study Procedures Table 9/1/2020 10:46 AM

2.0

* Will Usual Care Procedures/Interventions be used?"

Yes No

If yes, please specify and include a description of what the usual care or expected level of care is at VAPHS (e.g., medications, testing, timing, etc.) for patients, similar to those individuals that meet the inclusion/exclusion criteria for this research study:

A typical outpatient with Cocaine Use Disorder will be recommended to participate in group and/or individual psychotherapy targeting problematic substance use. Contingency Management (CM) is also frequently recommended for such patients. At VAPHS, CM involves twice weekly urine-based drug testing (point-of-care and confirmatory urinalysis) for chances to win abstinence-contingent reward.

All participants will receive treatment-as-usual during the 12-week treatment interval, which will be defined as recommended participation in at least two outpatient group and/or individual psychotherapy encounters within CTAD per week; participants will additionally continue pharmacotherapy for substance use and/orother mental health conditions, if applicable. The majority of participants will also receive one of two different versions of CM, already used within the VA (specifically, VoucherPBCM or TangiblePBCM).

2.1

If Usual Care Procedures/Interventions will be used, who is the individual or entity responsible for relevant aspects of the usual care (i.e., which of the above usual care activities will the research study team be responsible for)?:

The research study team will specifically be responsible for the delivery of CM within the context of the current study. The PI currently serves as the local implementation coordinator and primary provider of CM at VAPHS. She will oversee this aspect of usual care in consultation with the National CM

Implementation Team, as well as other CTAD providers. CM will be delivered by one or more research interventionists trained by the PI and supervised in consultation with her mentor(s).

2.2 Does the usual care at VAPHS for the condition of interest in this research study differ from national guidelines/recommendations (i.e. standard of care)?

Yes **No**

If yes, please describe the differences:

2.3 Are any procedures that are considered standard for this patient population performed more frequently than usual care?

Yes **No**

If yes, please indicate which time points are considered usual care and which are considered research.

2.4 If there is more than one standard, does VAPHS limit which one is followed (e.g. warfarin use for atrial fibrillation vs. one of the newer anticoagulants).

Yes **No**

If yes, please explain:

3.0

* Does clinical expertise need to be enlisted?

Yes No

If yes, please provide the provisions for enlisting the services of a clinician with appropriate expertise and privileges to perform duties, if the investigator is not a clinician [i.e. reviewing the data, adverse events, and new study findings; also making required decisions to protect the health of the subject (e.g., stopping the participant's involvement in the study or determining when to notify the subject or the subject's health care provider of information that may affect the health of the subject)]:

It is possible that circumstances could present during the study that would require clinical expertise. While suicidal/homicidal ideation and behaviors are not a focus of the current study, it is always possible that an imminent threat to the safety of the self or other could be disclosed during study assessments or CM treatment visits. If this should occur, study activities will be discontinued and study personnel will respond to the mental health crisis. This may include contacting the patient's mental health provider and/or escorting the patient to the mental health walk-in clinic or emergency department with the assistance of VA police. If such symptoms are described over the phone (or during a video call), study

personnel will follow the VAPHS warm-transfer protocol and/or VVC e911 protocol. This protocol is designed to ensure a warm transfer of the call to either the Veterans Crisis Line or local emergency services. Study personnel will also contact the patient's mental health provider in such cases to ensure appropriate follow-up. Participants will be informed of the limits of confidentiality during the informed consent process for the study. Significance of risk will be assessed by the PI. Dr. Forster has substantial experience working with individuals at elevated risk of suicide/homicide and has managed mental health crises in both research and clinical settings.

During participation in study procedures, it is also possible that an incidental finding could occur. We do not anticipate that incidental findings are likely because we are not conducting assessments for clinical purposes, designed to identify new medical or psychiatric problems. For example, the EEG procedure we describe herein is different from that used by a neurologist and is not designed to inform diagnosis of brain-related disorders. However, if data collected from a participant are found to be anomalous in some way, we will notify the participant of this within one week and will also share the result with the participant's Primary Care Physician. Similarly, it is possible that we may identify a previously undiagnosed mental health condition during study interviews. If this should occur and the information is relevant to ongoing care, we will share this information with the patient's mental health treatment coordinator. Participants will be alerted to the protocol for handling incidental findings during the informed consent process.

4.0

Please upload any surveys, questionnaires, and data collection forms.

Document Description Version Number

View ACQ(0.01) 0.01
View ACT Version A(0.01) 0.01
View ACT Version B(0.01) 0.01
View Adverse Childhood Experiences(0.01) 0.01
View AIS(0.01) 0.01
View BL / FU Session Notes (0.01) 0.01
View CFCS(0.01) 0.01
View CM Fidelity Assessment(0.01) 0.01
View CM Prize Reminder Slip(0.01) 0.01
View CM Session Flowchart(0.03) 0.03
View CM Tracking Form Wks 11-12 Fri Start(0.01) 0.01
View CM Tracking Form Wks 11-12 Tues Start(0.04) 0.04
View CM Tracking Form Wks 1-2 Fri Start(0.01) 0.01
View CM Tracking Form Wks 1-2 Tues Start(0.05) 0.05
View CM Tracking Form Wks 3-4 Fri Start(0.01) 0.01
View CM Tracking Form Wks 3-4 Tues Start(0.04) 0.04
View CM Tracking Form Wks 5-6 Fri Start(0.01) 0.01
View CM Tracking Form Wks 5-6 Tues Start(0.04) 0.04
View CM Tracking Form Wks 7-8 Fri Start(0.01) 0.01

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View CM Tracking Form Wks 9-10 Fri Start(0.01) 0.01
View CM Tracking Form Wks 9-10 Tues Start(0.04) 0.04
View DCQ(0.02) 0.02
View Demographic Info Form(0.02) 0.02
View DTCQ (To Be Purchased)(0.01) 0.01
View Fagerstrom(0.01) 0.01
View List of Emotions(0.01) 0.01
View Mini_MoCA(0.01) 0.01
View POC Test Results(0.01) 0.01
View PPIS(0.02) 0.02
View PRMQ(0.01) 0.01
View SLUMS(0.01) 0.01
View SOCRATES(0.01) 0.01
View SPSRQ(0.01) 0.01
View SSS(0.01) 0.01
View TRQ(0.01) 0.01

View: 4.1 Research study methods: analysis Plan

1.0 * Please describe the analysis plan for the study (it is acceptable to refer to the sponsor/multi-site protocol for section if applicable):

Data Analytic Plan.

EEG Data Preprocessing. Data from both incentive delay and flankers tasks will be visually inspected and band-pass filtered using parameters specific to each analysis. Data will subsequently be corrected for ocular, movement, and (if applicable) line noise artifact, using independent components analysis or possibly other methods. If necessary, bad channels will be replaced with interpolated data. Data from each task will be segmented into event-locked epochs. Epochs with significant residual artifact will be rejected and a current source density transformation may be applied to improve spatial resolution, prior to analysis, if deemed necessary. Alpha suppression will be computed for the pre-feedback reward anticipation interval in the Incentive Delay task by computing event-related spectral power in the alpha band (8-12 Hz), relative to a pre-response baseline interval. Differential alpha suppression to high magnitude tangible versus voucher prizes will be quantified at occipital sites (O1, Oz, O2) within the 1500 ms time window preceding feedback. For the Flankers task, ERN and conflict N2 amplitudes will be determined as follows. For response-locked event-related potentials, the negative peak amplitude of the difference wave computed for error vs. correct responses at sites FCz and/and Cz will be used as the measure of ERN amplitude. The sum of differences in stimulus-locked N2 amplitude between congruent vs. intermediate incongruity conditions and congruent vs. high incongruity conditions will be used to quantify parametric modulation of conflict N2 by differential control demands. For functional connectivity analyses, data will be bandpass filtered into targeted frequency bands (e.g., delta, theta, alpha, beta, and gamma). Theta frequency synchronization between ACC electrode sites (e.g., Cz, FCz) and lPFC electrode sites (e.g., F3, F4, F5, F6) will specifically be evaluated for error vs. correct and congruent vs. incongruent trials using synchronization likelihood or a similar approach. Exploratory

network level analyses may also be conducted for event-locked epochs from both Incentive Delay and Flankers tasks. In addition, based on exploratory findings from our pilot effort (Pro1787) we may additionally conduct exploratory analyses of our brief pre-task baseline (resting-state) EEG recordings including quantification of eyeblink rate and related metrics from EOG and EEG and channels.

Cognitive-Behavioral Data Preprocessing. In the Personalized Delay Discounting task, switch points will be determined for each participant based on decision outcomes for trials in each condition (with personally-relevant event tags, without personally-relevant event tags) and latency. Switch points represent the monetary amount at which a switch from immediate preference to delayed preference (or vice versa) takes place, suggesting similar subjective valuation of immediate and delayed amounts in that context. Next, a hyperbolic discounting model will be fit to switch point data on an individual subject basis to determine the discounting slope parameter, k. The difference in the natural log of k for event tag versus standard (no event tag) discounting conditions will subsequently be computed for each subject as an index of self-controlled decision-making in the context of episodic future thinking. No preprocessing is necessary to compute Brown-Peterson test scores; the total score (sum of all correct responses) will be used as the primary index of performance.

Pupillometry Data Preprocessing. Pupillometry data may also be acquired during participant engagement with computerized experimental paradigms and/or pre-task baseline EEG recordings. These data will be pre-preprocessed utilizing standard methods under the direction of co-investigator, Dr. Steinhauer, in preparation for additional exploratory analyses.

Power Analysis and Sample Size. In analyses of baseline predictors of treatment response in CM recipients (estimated n = 119-140) and long-term (i.e., six month) outcomes (estimated n = 105-140), using the statistical rule of thumb of needing 10 observation per predictor, our originally projected sample size would provide adequate power to include 10-14 variables in regression-based analyses. Random Forest methods are further supported for an expanded set of variables, as this highly flexible and powerful approach has been validated in "wide datasets," wherein the number of predictors exceeds the number of observations. With the anticipated enrollment of 140 participants, there will additionally be adequate power ($\beta = 0.20$, alpha = 0.05) to detect an effect size of $f = 0.12$ for the treatment adherence (adherent, non-adherent) X time (baseline, follow-up) interaction, supporting planned comparison of treatment-related change in neural and cognitive-behavioral measures between PBCM adherent and non-adherent Veterans. Assuming 15% attrition, the estimate of the detectable effect size for the treatment X time interaction for a total sample size of 119 is $f = 0.13$. The anticipated effect size of treatment-related change in synchronization likelihood between ACC-lPFC electrode sites is not known. However, previous work has established a medium-to-large effect size for treatment-related change in the ERN and N2 (in association with cognitive training).[74,75]

It was necessary to revise our original analytic plan to accommodate a smaller sample size than that originally projected. Recruitment under the current protocol was initially delayed due to institutional barriers that prevented timely acquisition of our EEG system. While recruitment was promptly initiated after our equipment was finally received, approximately three months later, all research activities were suspended due to risks posed by the COVID-19 pandemic. Due to the collection of EEG data and the nature of the interventions under study (e.g., need to be in the physical presence of the prize cabinet to potentially benefit from the increased psychological proximity of reward), it was not possible to convert the current protocol to be conducted fully remotely during the pandemic. A series of administrative

holds on research activities therefore effectively suspended enrollment for approximately one year. After research activities could be safely resumed, the COVID-19 pandemic also continued to negatively impact recruitment as the majority of outpatient substance use treatment services continued to be offered remotely throughout the remainder of our active enrollment period. This resulted in reduced foot traffic through clinic areas, making it more difficult to connect with potentially eligible participants. While a variety of new recruitment methods were introduced, our final sample size was much smaller than originally projected.

To address limitations related to the ratio of observations to predictors in the context of our reduced sample size, we revised our predictive analytic approach (Specific Aim 1) to prioritize model stability and interpretability, while framing results as more preliminary in nature. With respect to Aim 1, a revised sample size of ~50 participants was identified as sufficient to support investigation of up to five candidate predictors: e.g., two EEG-derived metrics, one clinical measure, one neurocognitive measure, and treatment condition. Recent simulation-based work (Austin & Steyerberg, 2015) further suggests that as few as two participants per predictor may be adequate, supporting investigation of the original candidate set even within the reduced sample. Two consulting biostatisticians endorsed this revised approach and further recommended modeling repeated binary outcomes over the course of CM treatment to improve power. In line with this recommendation, we modeled 24 repeated binary outcomes per participant, yielding up to 24 x n observations across n participants. However, recognizing that the effective number of independent events remains tied to the number of participants rather than the number of observations, we adopted a two-stage variable selection process to reduce the risk of overfitting. In the first stage, we screened predictors using single-predictor longitudinal logistic regression models, identifying those with theoretically plausible associations with the outcome. This process narrowed our total number of candidate predictors. In the second stage, we applied stepwise forward selection guided by the Akaike Information Criterion (AIC) to construct a parsimonious, interpretable multivariate model. To further assess model robustness and generalizability, we evaluated predictive performance using leave-one-out cross-validation (LOOCV).

Implications of our reduced sample size were also considered for Specific Aim 2, which involves longitudinal analysis of change in key neurocognitive metrics with adherence and abstinence as potential covariates. Based on guidance from statistical consultants, a sensitivity analysis indicated that a total sample size of 36 participants with both pre- and post-treatment data would provide adequate power to detect small to medium effect sizes (f = 0.17–0.30). This revised projection reflects the practical constraints of the available sample while maintaining sufficient power for detecting meaningful change over time in the context of repeated measures analysis. As an alternative analytic strategy, a median split approach to adherence and abstinence may be considered if data suggest that dichotomization would enhance interpretability or improve model stability in the context of limited sample size. While treating these variables as continuous covariates is generally preferred due to increased power and retention of variance, a binary approach may be appropriate in cases of non-linear relationships, bimodal distributions, or when simplifying the model structure offers clear interpretive advantages.

Specific Aim 1. Evaluate the utility of EEG and cognitive-behavioral measures of FMDM as predictors of differential treatment outcomes in TangiblePBCM versus VoucherPBCM. A significant interaction between CM treatment condition (i.e., TangiblePBCM versus VoucherPBCM) and neurocognitive indices

of FMDM function (i.e., EEG and cognitive-behavioral measures) is hypothesized. Specifically, individuals demonstrating greater FMDM impairment (poorer working memory function, less reduction in delay discounting with inclusion of future event tags, and reduced EEG/ERP signaling to abstract future reward and control demands) will achieve better outcomes in Tangible PBCM, relative to VoucherPBCM (Hypothesis 1a). In models including PBCM treatment condition as a factor, inclusion of EEG and cognitive-behavioral predictors is expected to significantly reduce prediction error with respect to both PBCM treatment response and long-term outcomes. Differential alpha suppression in response to tangible prize versus voucher prize rewards, in particular, will assay engagement by different types of future reward utilized in TangiblePBCM and VoucherPBCM. Consequently, differential alpha suppression is expected to be an especially robust predictor of outcomes in existing PBCM variants. It is further hypothesized that this candidate neuromarker will be selected for inclusion in a readily translatable predictive model – even when incorporating resource constraints that penalize predictors derived from more costly procedures (e.g., EEG incurring a greater cost-based penalty than self-report measures; Hypothesis 1b).

The proposed design affords measurement of all candidate predictors prior to initiation of PBCM, as well as monitoring of both CM treatment response and long-term outcomes for all CM recipients. Predictive models of CM treatment response and long-term outcomes will be developed separately, with the caveat that our revised final sample size may not support the latter. Candidate predictors will include pretreatment FMDM-related EEG (concrete versus abstract alpha suppression, ERN amplitude, parametric N2 amplitude effect) and cognitive-behavioral measures (Brown-Peterson score, $\Delta \ln(k)$), as well as clinical indicators (e.g., craving severity, past month cocaine use, number of previous treatment episodes)) and self-report scores. In order to examine the interaction between candidate predictors and CM reward parameters, PBCM condition (TangiblePBCM versus VoucherPBCM) will also be considered as an explanatory variable in predictive models.

I will receive focused training in predictive modeling, with an emphasis on recursive partitioning machine learning methods: classification and regression trees (CART) and random forests (RF). Our original analytic plan proposed that regression trees would be grown to examine the predictive structure of explanatory variables (including PBCM treatment condition) with respect to the following continuous outcomes: (1) % cocaine-negative urines during CM, (2) % CM sessions attended, (3) % days of any self-reported substance use during CM, and (4) % days of self-reported stimulant use during the 6 months following CM. CART involves partitioning observations into more homogenous subgroups with respect to the outcome of interest by identifying cut points along predictor variables. For each CART, cost-complexity pruning would be conducted using five-fold cross validation to limit overfitting. A Random Forest (RF) approach would subsequently be implemented with each set of predictors and outcomes to objectively evaluate the relative importance of each predictor and optimize overall model performance. RF involves growing an ensemble of decision trees based on bootstrapped samples of observations and predictors to increase tree diversity. This method includes internal cross-validation using out-of-bag error rates (based on observations not included in the bootstrap sample) to limit overfitting during model training and performs well without excessive tuning of model parameters. Taken together these data mining approaches would provide deep insight into interrelationships between predictors and outcomes of interest and could also be further examined through aa resource-constrained Tabu search procedure to develop multiple regression models forecasting treatment response (% cocaine-negative urines) in each PBCM variant, while penalizing individual predictors based

on measurement cost.103 Resource-constrained Tabu search has not previously been used to analyze the predictive utility of neuromarkers in view of the increased cost of measuring these signals but is ideally suited to this issue in measurement-based care. In our revised approach, we employed longitudinal logistic regression as described above and specifically examined outcomes on a per session basis, with provision of a cocaine-negative specimen at the session being considered a successful outcome and cocaine-positive or missing specimens considered unsuccessful. This revised approach enables more efficient use of the available data by capturing the full trajectory of participant responses over time through repeated measures modeling, rather than relying on a single aggregated outcome.

Missing Data Strategies: Recursive partitioning approaches (CART, RF) flexibly handle missing data for candidate predictors through several heuristic and/or interpolation based approaches. Missing data handling for TABU search is not yet well-characterized but works well, provided that missing data is randomly distributed and relatively rare. Expecting a 15% rate of attrition, usable substance use outcome data is anticipated for a minimal sample size of n = 119 CM recipients. Additional outcome variables will be derived from chart review (e.g., treatment engagement, urinalysis results), providing additional options for quantifying outcomes, not contingent on participation in study check-in appointments. Importantly, all methods specified above can be used with binary outcomes (i.e., CM-completer versus CM-non-completer). Consequently, while efforts will be made to collect detailed outcome data on each participant (and this appears feasible on the basis of my ongoing pilot project), primary predictive modeling aims can be accomplished under circumstances of high attrition and data loss. Our revised analytic approach has also been configured to be resilient to missingness through handling missing specimens as unsuccessful outcomes using an intent-to-treat approach. Where necessary (e.g., for treatment trajectories impacted by the pandemic), a Bayesian logistic regression model can also be used to impute missing values based on observed patterns to estimate likely values for unobserved responses.

Specific Aim 2. Evaluate longitudinal change in cognitive-behavioral and EEG-based indices of FMDM during CM. Engagement in PBCM will be associated with differential enhancement of control-related theta synchronization between ACC and lPFC during high conflict events in the Parametric Conflict Flankers task, relative to PBCM nonadherence and will also foster greater improvement in working memory and episodic future thinking effects on delay discounting (Hypothesis 2a). Individual differences in treatment response trajectory during CM will also be explored as a factor in neuroadaptive change during treatment (Exploratory Sub-Aim).

Increased functional connectivity within control-related brain networks in conjunction with CM would reflect important mechanisms of neural recovery facilitated by this intervention. I will receive training in functional connectivity analysis of EEG data, which may include a series of learning experiences guided by my co-mentor, Dr. Siegle, and consultants, Drs. Hetrick, Kim, and Sporns. Most importantly, I will receive training in synchronization likelihood, a nonlinear approach to estimating functional connectivity which measures statistical dependencies in dynamic time series and can thus characterize both linear and nonlinear interdependencies in EEG data. This technique may be applied to evaluate synchronization strength between pairs of electrodes and within frequency bands, based on a priori hypotheses, although more traditional functional connectivity measures may also be utilized. Specifically, theta frequency synchronization between ACC and lPFC electrode sites will be computed to quantify transient network dynamics related to control modulation. Treatment-related change in

executive working memory and delay discounting behavior will also be evaluated as cognitive-behavioral indicators of FMDM-related function.

Repeated measures analysis of covariance (ANCOVA) will be conducted to evaluate treatment-related change in the following indices of FMDM between PBCM adherent and non-adherent: (1) control-related theta synchrony between ACC and lPFC, (2) Brown-Peterson working memory score, and (3) change in the episodic future thinking effect in delay discounting slopes (Δ ln(k)). A general linear model design will be utilized including assessment latency (baseline versus follow-up) as a within-subjects factor. In order to account for differences in substance use, adherence, and PBCM treatment condition, these factors (% days of use, % sessions attended, PBCM condition) may also be considered as covariates or between-subjects factors using a median split approach. Tukey's HSD (or equivalent) will be used for post hoc evaluation of marginal means to clarify main and interaction effects. Adjusted marginal means may be used to investigate covariates as moderators of the treatment-by-time interaction. Given the previously identified relationship between ACC-lPFC theta phase synchrony and amplitude of the ERN and conflict N2,66,67 treatment-related change in these ERPs may also be evaluated using the same approach. Correlations between ERN/N2 amplitudes and ACC-lPFC theta synchrony, as well between EEG and cognitive-behavioral measures, may also be computed for each timepoint to identify significant linear relationships between dependent measures. To account for the constraints of a reduced sample size, we may employ alternative statistical approaches as needed—particularly to address non-normality and other assumption violations that could compromise model validity.

Additional exploratory analyses may also be conducted to investigate trajectories of recovery during PBCM in relation to neuroadaptive change. I will receive specialized training in multilevel modeling approaches to longitudinal data analysis, including use of growth mixture models to resolve latent subgroups exhibiting distinct patterns of longitudinal change. For participants assigned to both PBCM conditions, longest duration of cocaine abstinence may be computed on a weekly basis from within-treatment urinalysis results and attendance (unexcused, missed appointments will also be considered to end a period of abstinence). Growth mixture modeling may subsequently be employed to evaluate intra-individual change in the longest duration of abstinence achieved during PBCM treatment and determine if distinct change profiles meaningfully represent inter-individual variance. If identified, subgroups exhibiting distinct trajectories in PBCM may also exhibit different patterns of neural recovery within functional connectivity networks underlying cognitive control and reward representation. Exploratory, network-based analyses may therefore also be conducted (if applicable) and may generate new insights into neuroadaptive processes that reflect and may also support sustained abstinence in CM. Cocaine users have previously been demonstrated to exhibit reduced interhemispheric functional connectivity within the dorsal frontoparietal control network, which is thought to support goal-directed top-down control of attention and behavior, as well as representation and anticipation of future rewards. My training in functional connectivity analysis of EEG data will support exploratory analysis of network-level disturbances in CUD, as well as potential treatment-related change in interhemispheric functional connectivity within the dorsal frontoparietal control network in relation to CM. Using methods previously described by my consultants, Drs. Hetrick, Kim, and Sporns, I may also employ synchronization likelihood to identify localized functional connectivity networks that significantly differ between CUD subgroups exhibiting different patterns of cocaine abstinence during CM. Briefly, pairwise synchronization likelihood will be computed between all pairs of EEG channels for reward- and control-

related epochs derived from Incentive Delay and Flankers tasks, respectively. Non-parametric, network-based statistics will subsequently be employed to identify pairings which differ significantly between CUD subgroups at baseline and follow-up, including potential differences in interhemispheric functional connectivity within the dorsal frontoparietal control network. Training offered by my consultants would also afford the opportunity to combine synchronization likelihood with graph theoretic approaches to functional connectivity analysis. Consequently, additional exploratory analyses can target differences in network-level properties within local (e.g., strength, local efficiency, betweenness centrality) and global (e.g., path length, small worldness, global efficiency) functional connectivity structures. However, it is noted that additional exploratory analyses can only be undertaken if the final sample size is sufficient to support them.

Missing Data Strategies: Individuals lost to follow-up will be excluded from these analyses due to necessary inclusion of longitudinal measures from the follow-up timepoint. It is anticipated that covariates of interest will be available for all individuals who complete the follow-up assessment session. Specifically, treatment engagement will be determined on the basis of chart review and self-reported substance use will be evaluated on a weekly basis. For participants who miss one or more check-in assessment during the treatment period, the timeline follow-back procedure will be extended to evaluate the full period between the present and previous study contact. In my previous longitudinal study of substance users, I was able to collect all necessary follow-up data on 80.8% of my originally enrolled sample. However, it is also possible that unexpected circumstances may require imputation of missing data values. In such cases imputation of missing values will leverage available within- and between-subjects data.

Additional exploratory analyses and quality assessment analyses will also be conducted over the course of the study. Consequently, the analysis plan outlined above will not cover all analyses that may be potentially undertaken with the current dataset. Similarly, additional approaches to data preprocessing (filtering, data reduction, artifact rejection, etc.) that are not described above may also be applied in order to optimize signal quality for the purposes of proposed and exploratory analyses. It is noted that, because of the nature of the current study (human subjects research, psychophysiological research), data points may not be reliably collected as prescribed for all participants and timepoints. For example, missing data may occur if a participant chooses to discontinue study procedures during an assessment visit due to fatigue or external obligations. Data loss may also occur due to equipment failure or other conditions results in poor quality data during psychophysiological recordings and cognitive-behavioral testing procedures.

View: 5 Sub-Studies

1.0 * Is there a sub-study or are there sub-studies associated with this study?

There is a sub-study (or there are sub-studies) associated with this study and VAPHS is participating.

View: 5.1 Sub-Studies

1.0 * Please describe the sub-study or sub-studies:

SUB-STUDY 1: FEASIBILITY OF CM TREATMENT VIA TELEHEALTH TREATMENT SESSIONS

Due to the current COVID-19 pandemic, it is possible that noncritical in-person outpatient visits will be discontinued if there is a surge in new cases in our local area. Given the nature of the current RTC, we are at risk of substantial data loss if CM treatment sessions offered through the current protocol must be terminated (as was the case in 3/2020). We would therefore like to conduct a sub-study to test the feasibility of conducting CM sessions via telehealth treatment sessions. Specifically, we will experiment with methods for delivering CM via VA Video Connect sessions. One or more Veterans will be provided with oral fluid point-of-care tests and will be trained on how to perform this type of objective testing during VVC sessions such that results can be remotely reviewed and prize draws rewarded accordingly. Participants in this case study will receive the standard voucher version of PBCM offered at VAPHS and prize vouchers will be delivered to or retrieved by Veteran following the remote session. Participants will additionally be asked to provide feedback on home-based point-of-care testing, methods for remotely conducted CM prize draws, prize transmissal, and other related aspects of remotely-delivered CM treatment. As described in the Substudy consent form, a combination of remote and in-person treatment sessions may be offered, depending upon the unique needs of each participant and/or barriers to remote implementation that may present over time.

Between 1-15 Veterans will be invited to take part in telehealth-based CM treatment sessions. We will specifically make an effort to invite individuals to participate for whom in-person CM sessions are not preferred because (1) the Veteran is at high risk for complications from COVID-19, (2) the Veteran is under quarantine due to COVID-positive status or housing-related restrictions, or (3) the Veteran has ongoing transportation problems that make attending in-person treatment sessions more difficult. All participants will be either be self-referred or clinician-referred to receive CM services and will meet general requirements for this type of treatment (e.g., ongoing problematic stimulant use). Participants must also be willing and able to participate in telehealth services, appropriate for telehealth care, and able to interact and communicate through audio and visual elements of the VVC platform. No other eligibility criteria will apply. Participants in the substudy may be former (e.g., completed or withdrawn) participants from the primary protocol or participants determined ineligible to participate in the primary protocol. Participants will not receive any compensation for participating other than prizes received in the course of treatment. Aside from the use of VA-approved telehealth technology to remotely conduct CM treatment sessions, the CM protocol to be used in this substudy will be identical to that prescribed by VHA's National CM Implementation effort. Importantly, similar adaptation of evidence-based treatment protocols to telehealth are (and have been) routinely conducted in the course of standard clinical care during the pandemic. There are also no significant risks associated with the proposed telehealth-based protocol - rather, it is expected that this CM option may be lower risk for some Veterans. Potential participants will be informed of this opportunity during either interactions with the research team regarding in interest in the primary protocol (e.g., upon screening out) or during initial clinical interactions upon referral to CM if barriers to in-person attendance are identified. Participants will provide informed consent to participate in this substudy. Data collected will generally be limited to information typically acquired in the course of standard clinical administration of CM (i.e., self-reported use, substance use test results, attendance, etc.). However, we will additionally take note of any feedback from patients regarding the telehealth experience, as well as any technical or logistical problems that occur in the course of remote administration. The goal of this substudy will be to develop and refine methods for remote administration of PBCM should this become necessary in the future. The standard CM note template will be used to document such sessions in CPRS. All data collected for this substudy can be extracted from documentation of treatment sessions entered in the chart.

Risks and Benefits: With respect to Substudy 1, participants will have the opportunity to receive a telemedicine version of CM that is not otherwise available at our site and this may benefit Veterans for whom remote treatment options are indicated or preferred. There are no significant risks associated with the proposed telehealth-based protocol - rather, it is expected that this CM option may be lower risk for some Veterans. This substudy will combine the use of an approved "standard of care" treatment option with approved VA telehealth technology (e.g., VVC) and so does not significantly deviate from standard clinical practice. However, due to the use of Veteran-administered oral fluid testing, this treatment protocol would currently only be permissible in the context of research. Participants will be informed of confidentiality and privacy considerations that are unique to telehealth at the start of each session (for example, ensuring that the Veteran has sufficient privacy in their current environment), as is typical of all such clinical interactions.

SUB-STUDY 2: REMOTE PHYSIOLOGICAL MONITORING FOR STATE-DEPENDENT PREDICTORS OF CRAVING AND USE

SUB-STUDY 2 Specific Aim: Establish feasibility of data collection using wearable sensors and identify promising physiological markers of stimulant craving and/or use between treatment encounters.

In this sub-study, I will leverage the existing infrastructure of my CDA research to collect supplemental physiological and activity data via wearable sensors to identify potential real time markers of craving and use. Participants will be recruited through our established recruitment pipeline. Following enrollment in the parent protocol, up to 45 participants will be invited to participate in additional physiological and activity monitoring during the first two weeks of the 12-week treatment interval. Individuals who decline to participate will be asked to share specific concerns contributing to this decision. Those who choose to enroll will be outfitted with a wrist-worn ActiGraph wGT3X-BT wearable activity monitor and Bluetooth-enabled Polar H7 Heart Rate monitor. Together, these medical-grade wearable devices enable high resolution monitoring of heart rate (including R-R intervals), physical activity (including sleep/wake time and related metrics), and compliance without conveying feedback to the wearer. Participants will receive training on routine maintenance of wearable devices, including requirements for recharging/changing batteries. Feedback regarding acceptability of wearable monitoring, as well as problems encountered, will be recorded at the beginning and end of sub-study participation. Devices will be returned at the conclusion of the 2-week recording period, whereupon data will be downloaded and the participant will be compensated $40. Participants may additionally receive daily reminder calls during the 2-week recording interval to ensure that they are wearing the devices properly and to troubleshoot any problems that may arise. Upon request, participants may receive a copy of a clinical report, generated by ActiLife software, summarizing activity and sleep data from the recording interval.

Data Analytic Plan. The number of participants declining to participate in the sub-study, as well as feedback regarding acceptability of wearable device monitoring will be quantitively and qualitatively summarized. Data collected through ActiGraph/Polar wearable devices will be reviewed, preprocessed, and analyzed using ActiLife software. The proportion of data rejected due to noncompliance (detected using ActiLife's Wear Time Validation Tool) or poor electrocardiography (ECG) signal quality (determined through visual inspection) will subsequently be computed. Valid data segments will be subject to additional analyses investigating potential markers of high-risk states in wearable data streams. Based on previous work and known cardiovascular effects of stimulants, periods of elevated resting heart rate

are expected to predict self-reported stimulant use and subsequent stimulant-positive urinalysis. For example, periods of elevated heart rate associated with cocaine craving can be distinguished from use events based on duration (30-40 minutes for craving versus 2 hours for use). The number and duration of elevated resting heart rate intervals will be investigated as potential predictors of self-reported and objectively verified stimulant use using a mixed effects logistic regression approach. Additional exploratory features extracted from ECG and activity data (e.g., heart rate variability (linked to craving in alcohol users), sleep efficiency (known to be impaired during early cocaine abstinence), and number/duration of physical activity bouts) may also be considered. These preliminary analyses will serve to identify promising state-dependent markers from wearable data streams for future investigation. Importantly, a mobile interface to be developed under a separate protocol (Pro3566) will support ecological momentary assessment of craving, stress, and substance use and these data will critically inform future efforts to distinguish physiological markers associated with high-risk for use – of relevance to delivery of in the moment interventions – from actual use events.

View: 6 Study Population Summary

Study Population Summary

1.0 * What is the maximum number of subjects you plan to enroll at VAPHS?

215 (Target Sample Size Primary Study = 140; an additional 1-5 Veterans may be invited to participate in Sub-Study 1)

Participants in Sub-Study 2 (n = 45) will already be enrolled in the primary protocol and so are already included in the projected target sample.

2.0

* Do you plan on enrolling patients into different categories:

Yes No

If yes, please explain:

Participants who complete Screening and Baseline testing procedures will be randomized into two different conditions: VoucherPBCM (n = 70) or TangiblePBCM (n = 70. Details of the two study conditions are provided under Section 4. Healthy controls will either have no history of substance use treatment or will be considered to be in long-term recovery (i.e., having achieved > 1 year of abstinence from cocaine and other illicit substances). We will make an effort to match healthy controls to the patient sample based on age, sex, and smoking (nicotine use) status.

3.0 If this is a multi-site study, indicate the projected total subject accrual:

No.

4.0

* Please provide a justification for the sample size:

Power Analysis and Sample Size. In analyses of baseline predictors of treatment response in CM recipients (estimated n = 119-140) and long-term (i.e., six month) outcomes (estimated n = 105-140),

using the statistical rule of thumb of needing 10 observation per predictor, there will be adequate power to include 10-14 variables in regression-based analyses. Random Forest methods are further supported for an expanded set of variables, as this highly flexible and powerful approach has been validated in "wide datasets," wherein the number of predictors exceeds the number of observations. With the anticipated enrollment of 140 participants, there will additionally be adequate power ($\beta = 0.20$, alpha = 0.05) to detect an effect size of f = 0.12 for the treatment adherence (adherent, non-adherent) X time (baseline, follow-up) interaction, supporting planned comparison of treatment-related change in neural and cognitive-behavioral measures between PBCM adherent and non-adherent subgroups. Assuming 15% attrition, the estimate of the detectable effect size for the treatment X time interaction for a total sample size of 119 is f = 0.13. The anticipated effect size of treatment-related change in synchronization likelihood between ACC-lPFC electrode sites is not known. However, previous work has established a medium-to-large effect size for treatment-related change in the ERN and N2 (in association with cognitive training) [69,70]. We have also proposed to compare the treatment-seeking CUD sample to the approximately 45 healthy controls who may be invited to participate in a comparison sample. Data from controls would help determine how CM-referred veterans differ from healthy individuals with respect to approaches to rewarding abstinence. However, it was ultimately not possible to enroll a sufficient healthy comparison sample at our site. In addition, due to factors that negatively impacted participant accrual over the course of the current study (as described elsewhere in the protocol) a revised analytic approach was developed to make use of a sample size that was significantly reduced relative to that originally projected.

An additional 1-15 Veterans will be invited to participate in Substudy 1, with the goal that at least one individual completes a full course of treatment via telehealth. This sample size is reasonable for a case study and also reflects financial considerations which may impact the ongoing availability of oral fluid testing supplies for this purpose.

View: 6.1 Study Population

Study Population

1.0

* Check all that apply to describe your study population:

Study Population

Non-Veterans
Special Populations X
Veterans X
Vulnerable populations X
Other

2.0 * Indicate the inclusion criteria for enrollment:

▪ Military Veterans, ages 18-75

▪ DSM-5 Criteria for Cocaine Use Disorder (Mild, Moderate, or Severe)

▪ Cocaine Use Within Past 45 Days (or past 60 days if in a controlled environment for part of this time)

▪ Stated Goal of Cocaine Abstinence or Reduced Cocaine Use

▪ Normal or Corrected-to-Normal Visual and Auditory Acuity (e.g., patients with glaucoma or tinnitus may be eligible)

These criteria will be assessed prior to enrollment and it is noted that many participants will no longer meet all the above-stated criteria throughout the full study interval. For example, time since most recent cocaine use may exceed 45-60 days in patients who achieve and maintain abstinence during Contingency Management treatment and this would not be considered grounds for withdrawal from the study.

Healthy controls will either have no history of substance use treatment or will be considered to be in long-term recovery (i.e., having achieved > 1 year of abstinence from cocaine and other illicit substances). We will make an effort to match healthy controls to the patient sample based on age, sex, and smoking (nicotine use) status.

For Sub-Study 1, 1-5 Veterans will be invited to take part in telehealth-based CM treatment sessions. We will specifically make an effort to invite individuals to participate for whom in-person CM sessions are not preferred because (1) the Veteran is at high risk for complications from COVID-19, (2) the Veteran is under quarantine due to COVID-positive status or housing-related restrictions, or (3) the Veteran has ongoing transportation problems that make attending in-person treatment sessions more difficult. All participants will be either be self-referred or clinician-referred to receive CM services and will meet general requirements for this type of treatment (e.g., ongoing problematic stimulant use). Participants must also be willing and able to participate in telehealth services, appropriate for telehealth care, and able to interact and communicate through audio and visual elements of the VVC platform. No exclusion criteria will apply. Participants in the substudy may be former (e.g., completed or withdrawn) participants from the primary protocol or participants determined ineligible to participate in the primary protocol.

3.0 * Indicate exclusion criteria for enrollment:

▪ History of Severe Traumatic Brain Injury, Seizure Disorder, or other Neurological Conditions resulting in structural and/or functional abnormalities of the brain that are expected to reduce interpretability of (or acquisition of generalizable knowledge from) psychophysiological datasets

▪ Severe or Unstable Medical or Psychiatric Condition that may interfere with study participation or the ability to follow the intervention protocol (e.g., suicidality, untreated secondary substance use disorder, ongoing cancer treatment, potential for future/frequent medical hospitalization)

▪ Pregnant or Lactating Women

▪ Moderate-to-Severe Neurocognitive Impairment per Medical Record or SLUMS ≤ 20 or Mini MoCA ≤ 10

▪ In Long-Term Residential Treatment In a Controlled Environment or Imminently Expected to Enter Such Treatment During the Study Interval at the time of Screening

These criteria will be assessed prior to enrollment and it is possible that participants will experience a change in one or more of these criteria over the course of the study. For example, patients may be admitted to residential treatment or experience a medical hospitalization (unrelated to participation) during the study interval. In an effort to collect full and complete longitudinal data on as many participants as possible, such circumstances will not necessarily result in participant withdrawal from the study. However, if any such change is determined to adversely impact the risk-to-benefit ratio of continued participation, investigator-initiated withdrawal of the participant will occur.

It is further noted that individuals living in transitional housing will be eligible for inclusion. In addition, patients who are scheduled to discharge from a residential treatment program (e.g. CTAD CORE) will be considered eligible if they are not imminently expected to seek admission to another residential treatment environment upon discharge.

Healthy controls will either have no history of substance use treatment or will be considered to be in long-term recovery (i.e., having achieved > 1 year of abstinence from cocaine and other illicit substances). Healthy controls will be excluded if they test positive for substance use (e.g., based on breathalyzer test results or urine drug testing) at the time of the baseline assessment. An effort will be made to achieve a healthy comparison sample that is demographically similar to the patient sample and it is noted that otherwise eligible individuals may be excluded in order to achieve this objective.

4.0 If there are any age, ethnic, language, or gender-based exclusion criteria, including the exclusion of any pregnant or lactating women, or those of child-bearing potential, please provide justification:

Pregnancy and/or lactation may alter event-related potentials under study herein. As it will not be possible to systematically evaluate the influence of pregnancy/lactation on event-related potentials in the current design, there is scientific justification for excluding these individuals.

5.0 Please specify why vulnerable subjects and/or special populations will not be enrolled:

6.0 With some exceptions as listed in VHA Handbook 1200.05, incompetent subjects cannot be enrolled in VAPHS approved research. Specify that you will not enroll incompetent subjects and the general rules to be used in making that determination:

We will not enroll incompetent subjects in the current protocol. Competence to provide informed consent will be evaluated during the informed consent process. Those who are unable to provide informed consent will be excluded from the study.

View: 6.2 Study Population- Vulnerable Populations

Study Population

1.0

* Check all that apply to describe your study population:

Children
Decisionally Impaired
Economically Disadvantaged X
Educationally Disadvantaged
Prisoners

2.0 * Describe the precautions, and any additional safeguards that will be taken to protect the rights and welfare of vulnerable subjects if they are to be enrolled. Also note that certain populations may feel pressured or be vulnerable to coercion or undue influence to participate in research. Indicate any special considerations that may be taken for such groups:

We will not specifically target economically disadvantaged individuals in our recruitment efforts. However, it is possible that Veterans interested in participation and eligible for the current study will be from economically disadvantaged backgrounds.

Several safeguards have been established to minimize the risk of coercion or undue influence and to protect the rights of our participants.

Some potential participants will be informed of the study by one of their providers. This will allow participants to discuss concerns regarding participation with someone who is not directly affiliated with the study and who is oriented toward the needs of the patient rather than the study. We believe this will prevent patients from feeling pressured to participate in the current study. We also expect that the majority of potential participants will self-initiate contact with study personnel directly. In these cases the potential participant has already decided that he/she is interested in the study, which may offset the risk of coercion.

While we will provide monetary compensation for time and travel, we believe that study payments are reasonable and would not be considered to be coercive. Participants will also be educated that "informed consent is an ongoing process" and that they can choose to stop participating at any time without financial penalty or loss of benefits to which the Veteran would otherwise be entitled. Before each procedure, a brief description will be provided, including the rationale for the procedure as well as what the participant can expect to experience. Participants will be provided with an opportunity to ask questions prior to each study procedure and will also be informed that they may decline to begin a procedure if they feel uncomfortable in any way. They will also be reminded throughout that they may choose to end participation at any time, even if this requires terminating a procedure that is already under way.

View: 6.2.3 Economically Disadvantaged

Economically Disadvantaged

1.0 * Target Number of Participants:

140

2.0 * Please provide a justification for including these subjects:

We will not specifically target economically disadvantaged individuals in our recruitment efforts. However, it is possible that individuals of low socioeconomic status will be identified as potential participants. Specifically, many patients with chronic substance use disorders are members of economically disadvantaged communities and substance use may also result in adverse consequences with respect to employment and income. Recruiting a representative sample of Veterans with substance use disorders is necessary to improve generalizability of the our findings and we would be unable to achieve a representative sample if we specifically excluded economically-disadvantaged individuals. We additionally note that the treatment under study (Contingency Management) has been demonstrated to be effective, regardless of income level [71].

View: 6.3 Study Population- Special Populations

Study Population

1.0

* Check all that apply to describe your study population:

Employee and Student Subjects
Investigators Clinical Population X

2.0 * Provide a justification for including these subjects:

It is possible that a potentially eligible participant will be a member of a clinical population seen by a study investigator. For example, it is possible that one or more investigators will be involved with administration of CM or other substance use treatment services through the Behavioral Health service line. Dr. Forster provided clinical services through the Center for Treatment of Addictive Disorders during active recruitment and the majority of patients who would be eligible for this study will likely be receiving care through this clinic. While subjects from these populations may be at an increased risk of coercion, study procedures have been developed to protect against this risk and are further described under Section 6.3.2. Importantly, patients will regularly be informed/reminded that research is optional and voluntary and that they will have comparable access to Contingency Management treatment if they choose not to participate in the current study.

View: 6.3.2 Investigators clinical population

Investigators clinical population

1.0 * Please indicate how you will minimize the potential for them to feel coerced to participate. Discuss how the potential confusion in roles will be addressed:

It is possible that a potentially eligible participant will be a member of a clinical population seen by a study investigator. For example, it is possible that one or more investigators will be involved with administration of CM or other substance use treatment services through the Behavioral Health service

line. While subjects from these populations may be at an increased risk of coercion, study procedures have been developed to protect against this risk. Specifically, all participants will be asked to provide written informed consent prior to undergoing study procedures and will have the option to voluntarily discontinue the study at any time. During the informed consent process, all participants will be informed of the following: "Your doctor may also be involved as an investigator in this research study. As both your doctor and a research investigator, s/he is interested both in your medical care and the conduct of this research study. You are under no obligation to participate in this or any other research study offered by your doctor. Before you agree to participate in this research study, or at any time during your participation in this study, you may discuss your care with another doctor who is not associated with this research study."

It is noted that some participants will initially receive information about the study from a clinician who is not a study co-investigator and will therefore have an opportunity to discuss participation with this unaffiliated provider. In addition, we anticipate that the majority of potentially eligible participants will self-initiate contact with the study. In such cases, potentially eligible participants would not be under the direct clinical care of a study investigator involved with CM until after they had evaluated their interest in the study and determined whether or not they wished to participate. However, it is possible that participants under direct clinical care by a study investigator could receive information about the study from that investigator in some cases. If this should occur, the investigator will identify that he/she is involved with the study but will arrange that the screening and informed consent process could be conducted by other study personnel if the participant prefers. The investigator will inform potential participants that such arrangements have been made in order to minimize confusion about roles served by the investigator, as well as any perceived pressure to participate. Study personnel will always take care to clearly delineate clinical versus research procedures in which participants may become involved and will make all participants aware that research involvement is voluntary and can be discontinued at any time. Importantly, patients will regularly be informed/reminded that research is optional and voluntary and that they will have comparable access to Contingency Management treatment if they choose not to participate in the current study.

View: 7 Risk/Benefit Assessment-Risks

Risk/Benefit Assessment-Risks

1.0

* Risk classification for this study (select one).

Minimal Risk X

Greater than Minimal Risk

2.0 * Basis for making the above recommendation:

The potential risks to subjects in the proposed research are minimal. The proposed work utilizes only noninvasive procedures that suggest a level of risk, comparable to that which is typically encountered in

daily life or in routine physical or psychological examinations or tests. Potential risks include 1) minor itchiness or irritation at EEG electrode sites, 2) distress or discomfort during interview and/or self-report assessments, and 3) loss of confidentiality of information collected in the context of the proposed research. Risks are specific to involvement in proposed research procedures. Participation in this study will not entail any additional therapeutic risk. There are no known contraindications to Contingency Management. Furthermore, patients will be informed that they may withdraw from the study at any time without penalty and will continue to have access to Contingency Management services through CTAD.

3.0 * Describe the safety precautions that will be taken to minimize risks/harms:

Participants will be informed of potential risks during the informed consent procedure and will also be informed of all measures to protect against these risks (detailed below under, Protection Against Risk). The risks associated with the proposed research are minimal and methods in place to protect against these risk have already been evaluated and approved by the VAPHS Institutional Review Board in the context of an ongoing pilot study using procedures described in the proposed research. Consequently, the measures in place to protect against risks in the proposed work are expected to be adequate. The Contingency Management interventions used within this study are already routinely used within the VA and are not associated with any additional risks. Participants will, however, be asked to report any change in substance use, mental health symptoms, or gambling behavior that they notice during Contingency Management; while we have no reason to expect such changes, these symptoms will be monitored in order to guard against unknown risks.

Participants will be informed of potential risks during the informed consent procedure and will also be told that they can discontinue the study at any time without penalty or loss of access to treatment services. Participants will be informed that they do not need to answer questions posed in interviews or on self-report questionnaires if they do not wish to. They will also be asked to report discomfort during the EEG procedure, such as itchiness on the scalp, around electrode sites. If discomfort or distress is reported during any study procedure, the participant will be asked if he/she wishes to discontinue the procedure. Procedures will be discontinued upon participant request at no risk of penalty. As private information will be collected as part of this study, there is a risk of loss of privacy and confidentiality. This risk will be described during the informed consent procedure. In addition, all electronic and paper data will be stored in an approved, secure location and will not be transmitted outside the VA. All possible efforts will be made to limit the inclusion of personally identifiable information on study-related documents. Personal identifiers will not be used to label study data. Participants will be assigned a study ID and this coded number will be used to identify all paper and electronic files related to study participation. The link between the participant ID code and participant name will be maintained in a single file which will be password-protected and accessible by key study personnel only; this file will also be stored behind the VA firewall in a secure location on the VA network. The participant ID code will not be included on informed consent documents or other paper forms that include identifiable information (e.g., contact information) and will be stored separately from documents labeled with a participant ID code. Participants will be informed of information that may be entered in their personal medical record as part of clinical care administered through the study; such information may include urinalysis lab results and Contingency Management progress notes. Participants will also be informed that they can continue with the research study even if they choose to discontinue Contingency Management and/or do not wish to provide urines that will be subject to lab-based urinalysis. It is additionally noted that

there are no known contraindications to Contingency Management. In the event that a participant assigned to treatment-as-usual expresses a self-assessed need to seek initiation of Contingency Management programming prior to conclusion of the 12 week treatment interval, the participant will be reminded that he/she can voluntarily withdraw from the study at any time.

4.0

* Provide details regarding the nature of each risk using the area provided below:

Risk Name

View Activity / HR Monitoring (GOLDSTEIN SUBSTUDY ONLY)
View Confidentiality
View Interviews
View EEG Recording
View Self Report Questionnaires

5.0 * Do you plan on using the research answering service: Yes **No**

If yes, please Upload the research answering service form:

6.0 If your study involves a treatment or intervention, please upload the Patient ID Card:

View: 7.1 Risk/Benefit Analysis-Potential Benefits and Alternatives

Risk/Benefit Analysis-Potential Benefits and Alternatives

Describe any potential for benefits to participants in this study:

1.0 * Direct and Indirect Benefits to Subjects:

There are no direct benefits to participants in the proposed research. However, it is noted that participants assigned to the TangiblePBCM condition will have access to a version of CM that (while already used within the VA) is not currently offered at VA Pittsburgh and may potentially benefit some patients more than VoucherPBCM (the version currently offered at our site). It is also possible that participants will learn new information about themselves through participation in study interviews, self-report questionnaires, or other procedures. Participants will also be informed that their participation may help others by improving our understanding of important mechanisms of action in Contingency Management (as well as substance use recovery, more broadly) and may additionally clarify individual differences that affect how people respond to existing variants of PBCM.

2.0 * Describe alternatives (research or non-research) that are available to subjects if they choose not to participate in this study:

The alternative to participation in the current protocol is non-participation. Veterans who choose not to participate will continue to receive treatment-as-usual and may be eligible for other research studies.

View: 8 Methods of Recruitment and Retention

Recruitment Methods and Materials used for Retention

1.0

* Select recruitment methods used on this study:

Mail Campaign X
Referral by independent source X
Advertising such as fliers, letters, or ads (newspaper, TV, radio) X
Web Site
Research registry
Selected from pre-existing records X
Pre-existing relationship with participants
Other

If Other Methods Specify:

Mail Campaign

1.0 * **Please specify whether an "opt-in" or "opt-out" recruitment approach will be used. If an "opt-out" approach is planned, please provide a rationale for why the IRB should approve this approach including an assessment of the level of risk of this study and a description of the direct benefit of this study to all participants:**
The mail campaign targeting potential treatment recipients will utilize an "opt-out" approach whereby Veterans will be invited to contact the study team if interested in participation and notified that they may be contacted by the study team if they have not responded within a specific timeframe (~1 month). Phone outreach will be conducted to confirm that the Veteran is not interested in participating.

We believe that an "opt-out" approach is justified for the current protocol for the following reasons:
(1) the current study involves minimal risk
(2) all participants stand to benefit by receiving an evidence-based treatment offered through the study
(3) those most likely to benefit from treatment offered through this study (i.e., individuals with motivational deficits that interfere with substance use treatment engagement and/or achieving and maintaining cocaine abstinence) are also least likely to self-initiate contact

with the study
team after receiving a letter.

As described further under #2 below, our mail campaign will involve outreach to Veterans identified as potentially benefitting from Contingency Management treatment. This will include Veterans recently referred to Contingency Management and those recently evaluated for substance use treatment services who have a diagnosis of Cocaine Use Disorder. This may also include Veterans who have previously participated in Contingency Management and those who have engaged with screening/prescreening activities but did not complete randomization into treatment. In addition, Veterans identified to have recently tested positive for cocaine via drug-alcohol urinalysis results documented in the electronic health record may also receive mailings. In such cases, Veterans known to the study team may be contacted directly by mail and those who are not known to the study team will initially receive outreach about the study through their provider but may also receive a follow-up mailing.

In addition, our proposed recruitment method also includes several safeguards to ensure that patient rights are protected. First, we will send a letter indicating that patients can self-initiate contact with the study team to express that they are either interested in or not interested in study participation. We will additionally specify that, if we have not heard from the patient by a specific date, the study team may initiate phone contact to confirm that the patient is not interested. Under these circumstances we will always proceed under the assumption that the participant does not wish to participate (i.e., they have opted out) but will contact them by phone to confirm that they do not wish to opt-in. We will keep a record of participants to whom letters have been sent (including the date specified for potential phone follow-up), as well as phone contact and screening records in a spreadsheet on a secure VA shared drive that can only be accessed by the study team. These records will be regularly reviewed to identify Veterans who have not self-initiated contact and are due for phone follow-up. Phone outreach will entail a maximum of three total outreach calls, of which a maximum of one voicemail will be left if the patient is not available. Letters notifying Veterans of potential phone outreach will be on VA letterhead and will be signed by Dr. Forster, who is well-known to many potential recipients as a provider within the CTAD clinic. Taken together, these precautions should be sufficient to address possible discomfort or suspicion that could arise from a "cold call."

2.0 * Specify how subjects will be identified and how study eligibility will be determined:

Veterans will be recruited upon outpatient treatment engagement through CTAD at VAPHS. The following methods will be used to identify potentially-eligible Veterans with CUD:

1) CTAD Initial Evaluations / Intake Assessments. All patients initiating treatment through CTAD (or beginning a new episode of care) complete an evaluation with a CTAD provider. CTAD providers will be encouraged to inform Veterans about the study if they meet criteria for CUD. If the Veteran is agreeable, the CTAD psychologist will forward his/her information to the study team for subsequent outreach. CTAD assessment clinic records will also be screened on a weekly basis and a mailing with study information will be sent to potentially eligible patients. Screening will include CTAD outpatient Initial Evaluations, as well as intake/screening assessments for the CTAD CORE residential program and Opioid Substitution Treatment Clinic (OSTC).

Established CTAD patients who have been referred to CM by a provider will similarly be provided with information about the study. Veterans who have previously participated in Contingency Management treatment, or who have recently tested positive for cocaine, may also receive information about the

study by mail. As individuals who have previously participated in CM may now be in long-term recovery, these individuals may also receive information about participation as a healthy comparison subject.

2) CTAD CORE Information Session and/or Announcement During Group Psychotherapy. The PI or other study representative may present information about the research study as an announcement during group psychotherapy sessions. Veterans interested in the research study will be provided with study contact information.

3) Advertisements. Study brochures will be placed in the CTAD waiting room, as well as other public areas around the VAPHS University Drive and H. J. Heinz campuses. Flyers will also be placed in several community locations to target Veterans not currently receiving care at VAPHS. Flyers or brochures may also be included in materials provided to Veterans admitted to the CTAD CORE residential treatment program. In order to recruit healthy controls, brochures will also be deposited in public spaces within the hospital as well as area Vet Centers and other Veteran-oriented organizations and social clubs.

4) Referrals from Providers. Providers in the behavioral health service line will be informed about the study and the CTAD CM program. These providers will be encouraged to identify patients with problematic cocaine use and either (1) provide these patients with a study brochure or (2) refer these patients for a CTAD Initial Evaluation, whereupon they will have the opportunity to receive information about the study, if appropriate. We may additionally conduct outreach to other clinics expected to identify Veterans with active cocaine use on a semi-regular basis. For example, Veterans who are actively using cocaine may be identified in the course of routine services delivered through the VAPHS Cardiac Rehab program or during pre-surgical evaluations. Making providers in these clinics aware of the study (as well as the availability of CM more generally) may improve Veteran access to relevant treatment if active cocaine use is incidentally identified.

5) Table with Recruitment Materials. The study team may additionally set up a table to advertise for the study with approval from VAPHS or other relevant entities. A table may be set up for recruitment purposes on VA grounds (e.g., University Drive Atrium) or may be hosted at a community-based recovery-oriented event (e.g., Overdose Awareness event at Veterans Place of Washington Blvd).

Efforts to identify and recruit potential subjects will always respect personal rights to privacy and confidentiality, as outlined in the HIPAA guidelines. Patients with substance disorders will be recruited through referrals from inpatient and outpatient Behavioral Health providers at University Drive and Heinz Campuses of VAPHS. Clinicians in relevant clinics will be educated about the study's entry criteria and will be instructed to provide potentially eligible participants with study contact information. In addition, we request a waiver to conduct pre-screening of veteran records as this will be necessary to meet our recruitment goals. Specifically, Dr. Forster (PI) or an authorized research assistant will identify potentially eligible participants by pre-screening veteran medical records in CPRS. Specifically, Veterans who are initiating services through the Center for Treatment of Addictive Disorders (CTAD) or beginning a new episode of care will be identified as these patients will be scheduled for an initial assessment through the CTAD Clinic. Assessment clinic records will be screened on an ongoing basis and a mailing

with a study brochure will either be sent to the patient or transmitted to the patient during an upcoming clinical contact. In the latter case, Dr. Forster or an authorized research assistant may contact the veteran's provider by phone or encrypted Outlook email in order to alert the provider that the veteran may be eligible for the research study and to facilitate transmitting study information to the provider if he/she agrees. If the patient is interested in the study, he/she may contact the study directly to set up an appointment. In this way, the burden on the clinician will be minimal and it will not be necessary to store PHI related to potentially-eligible participants.

All potentially-eligible individuals who are interested in the study will be screened for initial eligibility by phone (or in person, if preferred by the patient). Preliminary eligibility for the study will be assessed during a scripted interview with study staff. Veterans interested in the study will first receive detailed information about the study and will be asked to consent to the screening procedure (including access to relevant medical records). The screening interview will include questions about demographic (e.g., Veteran status, age, sex) and clinical information (e.g., substance use diagnoses, most recent cocaine use, history of neurological disease, etc.) relevant to eligibility. Prospective participants may also be asked to participate in a Mini MoCA cognitive screening at this time to assess eligibility - otherwise, this screening will take place at the first study visit for those eligible on the basis of the initial screening interview.

Veterans meeting general criteria will be invited to schedule an initial study visit involving informed consent and diagnostic interview procedures. Veterans who are ineligible will be informed that they may be eligible for other research opportunities and that exclusion from the research study does not preclude access to CM treatment through CTAD if this treatment option is deemed appropriate by their CTAD provider(s). We will specifically ask for verbal consent to access electronic medical records during the telephone screening procedure. Patients who prefer to participate in an initial screening in person will provide written informed consent to participate in screening procedures only and will also be asked to sign a HIPAA Authorization permitting access to relevant patient medical records. Access to records will be used to confirm information provided by potential participants during the initial screening procedure. We will avoid accessing information beyond that which is immediately necessary to evaluate preliminary study eligibility.

3.0

* Provide the location (or locations) of the sites where participants will be recruited:

Participants will be recruited within the Center for the Treatment of Addictive Disorders, as well as public spaces within the hospital and community, frequented by veterans. Brochures and flyers will be posted in public areas within VAPHS (e.g., clinic waiting areas, patient lounges, etc.) and may additionally be placed in clinical areas such as provider offices or group treatment rooms. In addition to Heinz and University Drive campuses, brochures and flyers may also be placed at local CBOCs, Vet Centers, and Vet Court / Veterans Justice Outreach locations, as well as community treatment locations (specifically, local Cocaine Anonymous meeting locations, needle exchange locations, Resolve Crisis Services, and community-based methadone clinics), community-based organizations or resources specifically targeting Veterans who may be in need of substance use treatment services (specifically, offices of Veterans Services at local universities, Soldier On, Veterans Leadership Program of Western

Pennsylvania), and local homeless shelters/half-way houses/transitional housing facilities (e.g., Light of Life, Shepherd's Heart, Recovery House, etc.).

4.0 Please include information regarding any advertisements (print, TV, radio, etc) that will be used to recruit subjects including a general description of where this information will be posted:

Brochure flip cards and flyers have been prepared in concert with the Office of Public Affairs and are included as attachments below. Brochures and flyers will be posted in public areas within VAPHS (e.g., clinic waiting areas, patient lounges, etc.) and may additionally be placed in clinical areas such as provider offices or group treatment rooms. In addition to Heinz and University Drive campuses, brochures and flyers may also be placed at local CBOCs and Vet Centers, as well as community treatment locations (specifically, local Cocaine Anonymous meeting locations, needle exchange locations, community-based methadone clinics, and the Office of Veterans Services at the University of Pittsburgh). Brochures for recruitment of healthy veterans may also be distributed to area Vet Centers and other Veteran-oriented organizations and social clubs.

5.0

Please UPLOAD the documents that will be used for recruitment and an introductory statement or letter to accompany consent for those studies obtaining written informed consent using methods such as fax, email or mail (if applicable). Please also upload any screening/recruitment questions that will be verbally asked of potential research subjects. Also, if you will be providing any retention materials, please upload them here.

Name Reviewer Modified Date Version Number

Appointment Reminder - WRAP BL Forster, Sarah Emily 10/17/2018 2:26 PM 0.01

Appointment Reminder - WRAP Follow-Up Forster, Sarah Emily 10/17/2018 2:27 PM 0.01

CM FAQ Document Forster, Sarah Emily 10/11/2018 7:31 PM 0.01

Contact Information Form Forster, Sarah Emily 10/17/2018 1:33 PM 0.01

Letter - Re-engage After Pandemic Hold Forster, Sarah Emily 9/1/2020 4:32 PM 0.01

Letter - WRAP Follow-Up Reminder Forster, Sarah Emily 10/17/2018 2:22 PM 0.01

Letter - WRAP Lost to FU Forster, Sarah Emily 10/17/2018 2:23 PM 0.01

Letter - WRAP Missed Research Appt Forster, Sarah Emily 10/17/2018 2:22 PM 0.01

Letter - WRAP Missed Treatment Appt Forster, Sarah Emily 10/17/2018 2:22 PM 0.01

A set of updated Recruitment letters dated 5/2/2022 has been uploaded with the current package.

Letter - WRAP Recruitment Other Evaluation Forster, Sarah Emily 1/13/2020 4:43 PM 0.02

Letter - WRAP Recruitment Outpatient Evaluation Forster, Sarah Emily 1/13/2020 4:44 PM 0.04

Letter - WRAP Recruitment Previous CM Forster, Sarah Emily 1/13/2020 4:43 PM 0.02

Letter - WRAP Recruitment Recent Referral Forster, Sarah Emily 1/13/2020 4:43 PM 0.02

Letter - WRAP Remote Screening Reminder Forster, Sarah Emily 9/1/2020 4:33 PM 0.01

Letter - WRAP Return Questionnaires Forster, Sarah Emily 10/17/2018 2:24 PM 0.01

Letter - WRAP Scheduling BL or FU Forster, Sarah Emily 10/17/2018 2:23 PM 0.01

Letter - WRAP Scheduling Check-In Forster, Sarah Emily 10/17/2018 2:23 PM 0.01

Letter - WRAP Screening Reminder Forster, Sarah Emily 10/17/2018 2:21 PM 0.01

Letter - WRAP Vendorization / Payment Forms Forster, Sarah Emily 10/17/2018 2:25 PM 0.01

PAO Approval Forster, Sarah Emily 9/27/2018 1:15 PM 0.01

WRAP Flier Forster, Sarah Emily 9/27/2018 1:05 PM 0.01

WRAP Flip Card Forster, Sarah Emily 9/27/2018 1:05 PM 0.01

WRAP Flip Card Printer Error Version Forster, Sarah Emily 8/26/2019 4:51 PM 0.01

Updated Recruitment materials have been uploaded with the current package, dated 5/2/2022.

View: 9 Informed Consent

Informed Consent

1.0

* Indicate the types of consent that will be involved in this study (check any or all that apply):

Informed Consent Category

Written/signed consent by subject

Waivers are being requested.

Verbal consent or written information sheet(Requires a Waiver of Documentation of Informed Consent - see below)

2.0

* Waivers: If you are applying for any waivers of consent (check any or all that apply):

X Waiver of Informed Consent

X Waiver of HIPAA Authorization

X Waiver of Documentation of Informed Consent (telephone consent, verbal script)

No Waiver at all

3.0 * Will this study include non-English speaking participants?

Yes **No**

View: 9.1 Waiver of HIPAA

You have indicated you are requesting a waiver of HIPAA.

1.0

* Is the request only for Screening/Recruitment purposes?

Yes No

If yes, please describe your screening/recruitment method:

Waiver for Telephone Screening

Potential participants will self-initiate contact with study personnel after being informed of the study by a provider, study advertisement, or mailing and will be asked to engage in a screening process. We anticipate that the majority of patients will participate in this screening process by telephone. We will specifically ask for verbal consent to access records in CPRS during the telephone screening procedure. Access to records will be used to confirm key information provided by potential participants during phone screening - namely, mental health and general medical diagnoses listed in the individual's CPRS Problems List. We may also check active consults and/or recent progress notes for evidence of referral to the Contingency Management program. As the Problems List may not always reflect current diagnoses, it may also be necessary to access other recent records in order to confirm information provided by potentially-eligible participants. We will avoid accessing information beyond that which is immediately necessary to evaluate preliminary study eligibility. We will only access information beyond that which is immediately necessary to evaluate preliminary study eligibility (e.g. progress notes and laboratory results tracking progress in CM) following provision of written HIPAA authorization at the initial study visit. Potential participants will be asked to verbally provide identifiable information which may be necessary to access CPRS records (e.g., name, last 4 of SSN) and/or establish future contact (preferred phone number). Such information will not be acquired from patient medical records directly. Minimal identifiable information will be maintained in a secure location for scheduling purposes.

Waiver for Pre-Screening Records

We also request a waiver to conduct pre-screening of veteran records. Specifically, Dr. Forster (PI) or an authorized research assistant will identify potentially eligible participants by pre-screening veteran medical records in CPRS. Veterans who are scheduled for an Initial Evaluation appointment through the Center for Treatment of Addictive Disorders (CTAD) be screened with respect to basic eligibility criteria, either before or after the time of their Initial Evaluation appointment. Veterans who have previously participated in Contingency Management and may therefore have interest/need to re-engage with this type of treatment may also be identified for pre-screening. Individuals who have recently tested positive for cocaine (e.g., within the past 3 months) may also potentially benefit from this type of treatment and may additionally be identified for pre-screening. When a potentially-eligible veteran is identified, Dr. Forster or an authorized research assistant will either (1) send out a mailing with study information (letter and brochure) directly to the patient if known to PI (e.g., if no further upcoming clinical encounters have been scheduled) or (2) contact that veteran's provider by phone or encrypted Outlook email in order to alert the provider that the veteran may be eligible for the research study. If the clinician agrees, Dr. Forster (or an authorized research assistant) will provide study information (i.e., letter and brochure) to the clinician for distribution to the patient during an upcoming clinical contact. If the patient is interested in the study, he/she may contact the study coordinator directly to set up an appointment. In this way, the burden on the clinician will be minimal and it will not be necessary to store PHI related to potentially-eligible participants.

Waiver for Initial Study Visit When Conducted Remotely

We are requesting to extend our waiver of HIPAA for telephone-based screening to the initial Consent and Screening appointment for the study in order to offer the option that this appointment be conducted remotely.

We will specifically ask for verbal consent to access records in CPRS during the remote study visit. Such access will be necessary to confirm information provided by the Veteran, document the research visit, schedule the first in-person visit, and facilitate coordination with other providers as needed. The participant will subsequently be asked to provide his/her written HIPAA authorization at the first in-person initial study visit as part of the process for obtaining written informed consent to participate in the study.

If no, the request is for the full study (e.g. retrospective chart reviews and certain observational studies)

Please describe the types of records and/or databases to be accessed:

We will review patient data in CPRS, as needed, to determine patient eligibility. We will begin by reviewing the Problems List and, if applicable, the recent CTAD Initial Evaluation report for the Veteran. It may also be necessary to review patient medications, recent DAU lab reports, psychiatric and medical reports, C&P reports, and clinical progress reports in some cases. In such cases, we will specifically target information in the record that may be necessary to determining eligibility and may specifically conduct a text-based search (e.g., for terms like "TBI" or "Traumatic Brain Injury") in order to check the patient's medical record against self-reported information provided during the screening interview. It may additionally be necessary to view the Veteran's upcoming appointments for scheduling purposes and/or enter study-related documentation into the chart.

THE IDENTIFIABLE INFORMATION BEING REQUESTED:

Note: If participants will be receiving payment and HIPAA Authorization is not being obtained, you must select Names, Addresses and Social Security Numbers as that information will be disclosed for payment purposes.

2.0

* Identifiable Information per HIPAA Definition

None
Account numbers
Biometric identifiers, including finger and voice prints
Certificate/license numbers
Device identifiers and serial numbers
Elements of dates (except year, for example, date of birth, admission date, discharge date, date of death, date of procedures; and all ages over 89)
Email Address
Fax Numbers
Full-face photographic images or any comparable images
Geographical subdivisions smaller than a State (street address, city, county, precinct, zip code, and their equivalent geocodes, except for the initial three digits of a zip code) X
Health plan beneficiary numbers
Internet Protocol (IP) address numbers
Medical Record Numbers
Name or any derivative of name such as initials X
Social Security Numbers X
Telephone Numbers X
URLs (Web Universal Resource Locators)
Vehicle identifiers and serial numbers, including license plate numbers
Any other unique identifying number, characteristic, or code (Note: The study ID number, code or other means of record identification is not considered one of the identifiers that must be excluded for de-identification)

3.0

* Patient Protected Health Information:

Demographic Information (e.g., Name, Address, Phone Number, Social Security Number X
Billing and Payment Information
Hospital or Medical Records X
History and Physical Exam Notes X
Mental Health Records X
Data Previously Collected for Research Purposes X
Progress Notes X
Consultation Reports X
Laboratory Test Results X
Operative Reports

Other
Please indicate the 'Other' Patient Protected Health Information:

4.0

Other Health Information:

Name

There are no items to display

View: 9.1.1 Waiver of HIPAA - More Information

Waiver of HIPAA- More Information

1.0 * Describe how the identifiable information is to be used and/or disclosed only by members of the research team and the following persons (identify with specificity and justify the need to disclose the information to anyone outside the VHA.) Note: If participants will be receiving payment and HIPAA Authorization is not being obtained, you must also describe this disclosure to representatives of the VA for administrative purposes here.

Also describe how this activity meets the “minimum necessary standard” described in the HIPAA Privacy Rule:

Identifiable information will only be accessed by members of the research team who are immediately involved in pre-screening records, conducting telephone screening, making determinations about study eligibility, scheduling participants, and conducting the initial Consent and Screening Visit. These procedures will generally be conducted by a single member of the research team (Dr. Forster or a research assistant working under her direction). However, it may be necessary to share identifiable information within the research team in some cases (e.g., if a difficult eligibility question arises). In effect, the minimum necessary information to assess eligibility will be shared with the minimum necessary people. Identifiable information will not be shared outside the study team or with anyone outside the VHA.

The proposed study poses minimal risk to the privacy of the subjects because...

2.0 * Describe how the identifiable information will be protected from improper use or disclosure by (detail how this will be accomplished including the limitations of physical or electronic access to the information and other protections):

A record of pre-screening, telephone screening, and initial Consent and Screening visit activities will be maintained in a password protected database, stored behind the VA firewall and will include minimal necessary identifiers to reference patient records (i.e. Last Name and Last Four of SSN). Only those immediately involved with pre-screening/screening and scheduling will have access to this spreadsheet.

3.0 * Describe how the identifiers will be destroyed at the earliest opportunity consistent with the research (discuss the timeframe or the reasons the identifiers must be retained, including health or research justifications or any legal requirement to retain them) (Note: At this time, identifiers used for

research screening and all other screening records must be retained indefinitely and this must be documented by checking “Other” below):

All research records will be maintained in accordance with the Veterans Health Administration (VHA) Records Control Schedule. Paper records will be disposed of using methods deemed appropriate by the VAPHS Privacy Officer, and all electronic data will be sanitized using methods rendered appropriate by the VAPHS ISSO.

* When will screening data be de-identified or destroyed:

Name

Other

If Other, please describe:

Research screening records and identifiers will be maintained in accordance with the records control schedule, as per VA requirements.

4.0 * Describe how the identifiable information will not be reused or disclosed to any other person or entity outside the VHA other than the manner described in the protocol, except as a required by law, for authorized oversight of this research study, or as specifically approved for used in another study by an IRB:

Identifiable information will only be accessed, reviewed, and maintained by study personnel who are immediately involved with pre-screening, screening, and scheduling. Identifiable information will not be shared with other persons or entities except in such cases that this is required by law or for qualified purposes of study oversight.

5.0 * Describe why the proposed study cannot be practicably conducted without a waiver of authorization: (discuss reasons why it would not be possible to obtain authorization from individual subjects. Time constraints themselves are generally not considered adequate for this justification:

Telephone Screening:

In the current study, potential participants will be asked to self-initiate contact with study personnel but many may fail to meet our general eligibility criteria. We do not have sufficient resources (e.g., funding, personnel, etc.) to conduct an in-person screening session with each individual who expresses interest in the study. Potential participants will be asked to verbally report information necessary to evaluate eligibility during the telephone screening. However, it is necessary to confirm this information in the electronic medical record in order to ensure that it is accurate. For example, potential participants may be unaware of diagnoses that would preclude study participation. If a rule-out is identified at the time of the initial study visit (rather than during the phone screening), this may present a significant inconvenience to the potential participant, who would have set aside time for the study visit and may have travelled a considerable distance to attend. Limiting the occurrence of these situations is thus in the best interest of both potential study participants and the research team. We will ask potential participants for verbal permission to access CPRS records in order to confirm information provided through self-report. Potential participants will have the ability to decline, at which point we would refrain from accessing their records.

Pre-Screening Records

In order to ensure that all patients who might be appropriate for the evidence-based treatment offered through this study are made aware of this treatment option/research study, we are requesting to pre-screen specific Veterans' medical records in order that they can be provided with study information. This is one element of a multi-pronged recruitment approach that was determined to be necessary in order to achieve the required sample size for the current study on the basis of recruitment feasibility information acquired through our earlier pilot project (Pro1787).

Due to the nature of the study, establishing contact through a potential participant's provider is preferable for several reasons. As described in Section 6.2 (Vulnerable Populations) engaging providers in the recruitment process will help us to identify appropriate participants and ensure that they can be recruited into the study without undue influence or coercion. Our target population is also unlikely to respond to study advertisements, such as flyers or newspaper ads, making provider referrals absolutely critical. Without enlisting the support of providers in the recruitment process, it will not be possible to meet our recruitment aims. Providers who have contact with the target population do not directly benefit from involvement in research activities and have limited time with which to engage in recruitment activities. A waiver of HIPAA for the purpose of pre-screening records is thus necessary.

Finally, we would like to offer the option to participate in our initial Consent and Screening visit through a remote modality such as telephone or video call. This will enable us to ensure that only those Veterans who are fully eligible to participate in the protocol are asked to attend an in-person study visit. While we will also take precautions to protect our participants and staff during in-person appointments to occur during COVID-19, it is preferable to conduct research activities remotely if and whenever possible.

6.0 * Describe why the proposed study cannot be done without the specified identifiable information: Discuss reasons why it would not be possible to conduct the research without the identifiable information being collected.

The Waiver of HIPAA is requested in order to pre-screen and screen veterans for potential study eligibility and, when necessary, conduct the initial Consent and Screening visit. Identifiers are thus necessary to ensure that the appropriate individual's records are accessed for review.

View: 9.2 Waiver of Informed Consent

Waiver of Informed Consent

1.0

* The proposed study poses minimal risk to the subjects because (outline the subject’s involvement in the project and why the study poses minimal risk):

Waiver for Pre-Screening Records

We also request a waiver to conduct pre-screening of veteran records. Specifically, Dr. Forster (PI) or an authorized research assistant will identify potentially eligible participants by pre-screening veteran

medical records in CPRS. Veterans who are scheduled for an Initial Evaluation or other Intake/Screening assessment appointment through the Center for Treatment of Addictive Disorders (CTAD) be screened with respect to basic eligibility criteria, either before or after the time of their assessment appointment. When a potentially-eligible veteran is identified, Dr. Forster or an authorized research assistant will either (1) send out a mailing with study information (letter and brochure) directly to the patient (e.g., if no further upcoming clinical encounters have been scheduled) or (2) contact that veteran's provider by phone or encrypted Outlook email in order to alert the provider that the veteran may be eligible for the research study. If the clinician agrees, Dr. Forster (or an authorized research assistant) will provide study information (i.e., letter and brochure) to the clinician or other CTAD representative for distribution to the patient during an upcoming clinical contact. If the patient is interested in the study, he/she may contact the study coordinator directly to set up an appointment. In this way, the burden on the clinician will be minimal and it will not be necessary to store PHI related to potentially-eligible participants.

2.0

* The waiver will not adversely affect the rights and welfare of the subjects because:

Pre-screening activities will be conducted to identify Veterans who might benefit from treatment offered through the study because these Veterans may not otherwise be made aware of this treatment option. Veterans will always have the right to decline treatment and/or research participation. In addition, Veterans may be able to receive CM treatment even if they choose not to participate. In this way, the primary consequence of the proposed pre-screening process will be to make Veterans aware of an empirically-supported treatment option that may be added to their standard outpatient substance use treatment programming to better support cocaine abstinence. If clinically appropriate, Veterans may engage with this treatment option either in the context of the current study or outside the context of the current study, if they decline research participation.

3.0

* The research could not reasonably be carried out without the waiver because:

Based on our earlier pilot project (Pro1787), we have determined that it will be necessary to add pre-screening to our recruitment plan in order to meet monthly recruitment goals. We estimate that it will be necessary to recruit approximately 5 Veterans per month in order to successfully complete the current project on schedule. We have also made changes to our eligibility criteria to improve the feasibility of our recruitment plan; however, prescreening will also be necessary in order to ensure that potentially-eligible individuals are more reliably provided with study information.

4.0 * The research could not practicably be carried out without using identifiable private information or identifiable biospecimens because:

Access to identifiable information will be necessary to track participant progress through the study protocol and private information derived from participant medical records (i.e., urine drug test results) represents a key outcome variable for the current study. In addition, delivery of Prize-Based Contingency Management (CM) requires that supervised urine specimens be collected prior to each

session and these specimens must be marked with identifying information in order to ensure that the correct specimen is tested at point-of-care during CM sessions and correctly documented in patient medical records following confirmatory processing by our on-site lab.

5.0

* When appropriate, subjects will be provided with the following additional pertinent information after participation (if you have no plans to provide additional information to subjects please provide justification):

Individuals who are prescreened will be provided with information about the study including contact information for study personnel. If these individuals contact study personnel to express interest in participation, they will be provided with additional pertinent information about the study during the screening process (see Screening Script).

View: 9.3 Waiver of Documentation of Informed Consent

Waiver of Documentation of Informed Consent

You have selected a waiver of Documentation of Informed Consent

1.0

This is a request for Waiver of Documentation of Informed Consent because this research study conforms to either A and/or B (Check if 'yes' and provide the verifying information requested):

* A: The only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern. Yes No

AND/OR

* B: The proposed study poses minimal risk to the subjects. **Yes** No

If yes, please explain why the proposed study poses minimal risks to the subjects. (Outline the subject's involvement in the project and why the study poses minimal risk) :

If yes, please explain why the proposed study poses minimal risks to the subjects. (Outline the subject's involvement in the project and why the study poses minimal risk) :

A Waiver of Documentation of Informed Consent is requested for the telephone screening procedure and initial Consent and Screening appointment only. Eligible participants will be asked to provide written informed consent during their first in-person study visit. During the screening procedures conducted by phone or video call, potentially eligible participants will be asked to answer questions necessary to evaluate study eligibility. They will be informed that they are not required to answer any questions they

do not wish to. Potentially eligible participants will also have the option of providing verbal consent for study personnel to access their medical record in order to confirm eligibility. Screening data will be maintained in a secured location for eligible participants. Data from ineligible participants, as well as those who do not subsequently provide written informed consent, will also be maintained in a secured location. In lieu of written consent at the time of the remotely conducted Consent and Screening visit, when applicable, the investigator will send a written consent form by mail. Participants who are determined through remote screening to be eligible and willing to enroll in the study will bring their signed consent form to the baseline appointment (the first in-person encounter) or will return the signed form by mail. If the signed form has not been received by the time of the initial in-person visit (either by mail or personal delivery by the participant), the participant will be asked to sign a new copy the consent form before any in-person research procedures commence. In this way, written informed consent will be documented by/at the time of the first in-person study visit.

2.0 * The research involves no procedures for which written consent is normally required outside of the research context. Research procedures include:

1.) Potentially eligible participants will be asked to listen to information about the study.

2.) Potentially eligible participants will be asked to consent to study personnel accessing their medical record in order to evaluate eligibility. They will have the option to decline.

3.) Potentially eligible participants will be asked to answer a series of questions in order to determine eligibility to participate in the study. Questions will focus on health and substance use history, as well as basic demographic data. They will have the option to decline to answer any question they do not wish to.

4.) Eligible participants will be asked to provide contact information and to schedule a study visit if they are interested in participating.

5.) Participants may also be asked to answer questions in the context of interview, cognitive screener, and/or self-report measures.

3.0 * Explain how whenever appropriate, the subjects will be provided with additional pertinent information (e.g. an information sheet):

Participants will provide written consent and will be provided with a copy of the signed study consent form, upon presentation at the first in-person study visit.

4.0

Please upload SCRIPT here:

Document Description Version Number

View Screening Script - Phone & In-Person Versions(0.06) 0.06

ID: Pro00002689

View: 9.4 Consent Forms & Process of Consent

Consent Forms & Process of Consent

1.0 Upload the completed forms into the correct lists below.

1.1

Informed Consent Form (clean copy):

Document Modified Date Version Number

View Goldstein Substudy Consent(0.03) 2/11/2021 12:00 AM 0.03

View Patient Consent(0.08) 11/16/2020 12:00 AM 0.08

View Telehealth Substudy Consent(0.03) 11/4/2020 12:00 AM 0.03

1.2

Provider Behavior Informed Consent Form (clean copy):

Document Modified Date Version Number

There are no items to display

1.3

Screening Informed Consent Form (clean copy):

Document Modified Date Version Number

View Screening Consent(0.08) 11/16/2020 12:00 AM 0.08

2.0

Consent Forms (modified copy):

Document Modified Date Version Number

View Goldstein Substudy Consent Tracked Changes(0.01) 2/12/2021 9:45 AM 0.01

View Patient Consent - Tracked Changes(0.04) 8/27/2019 1:16 PM 0.04

View Screening Consent - Tracked Changes(0.06) 10/9/2020 1:10 PM 0.06

A Healthy Comparison Subject Consent has now been added.

3.0 * Describe how, where, when, and by whom the consent process will be initiated:

The consent document(s) will be thoroughly and extensively reviewed with participants and we will allow sufficient time to make an informed, voluntary decision. For those adults who wish to involve a family member or friend in the consent process, we will arrange to do so. We will make it clear that the Veteran's decision to participate or not will have no effect on their treatment or relationship with the VA Healthcare System.

For the majority of participants, an initial eligibility screening will be conducted by telephone and written consent will not be provided at this time. (A Waiver of Documentation of Informed Consent has been requested to cover telephone screening procedures). However, it is possible that interested patients may also prefer to participate in the initial eligibility screening in person and, in such cases, a separate Screening Consent will be used to document written consent for initial screening procedures only and will also include HIPAA authorization . This document covers all information conveyed through the telephone screening script and will be thoroughly and extensively reviewed with all individuals who participate in in person eligibility screening. In person eligibility screening procedures will be conducted in a private interview room or office at the Research Office Building (Building 30) or a private office at Building 29.

Interested participants who are eligible on the basis of initial eligibility screening (either by phone or in person) will be scheduled for a separate appointment with a member of the research team, during which the informed consent document for the full protocol will be extensively reviewed for comprehension and witnessed oral and written consent to participate will be obtained. Potential risks and benefits from this research will be reviewed. This appointment will typically be conducted in a private interview room or office at the Research Office Building (Building 30) or a private office at Building 29. However, it is also possible that this appointment will conducted remotely if judged to be in the best interest of the Veteran. In such cases, written consent will then be obtained at the time of the first in-person visit for those who are eligible to continue on to baseline assessment and randomization. Participants will be provided with a copy of their signed consent form at that time.

Participants may be asked to consent to optional activity and heartrate monitoring (i.e., Goldstein Substudy 2) after they have been assigned to one of the two Contingency Management treatment conditions.

4.0

* Will you be maintaining a Master List of Subjects?

Yes

5.0 * Describe when the subject's name will be added to the master list and how the list will be maintained in a secure fashion.

A record of all participants screened for participation in this study will be maintained in our secure Dacima database; identifiable information will only be accessible to those with a need to view this information. Participants who have provided written, informed consent to participate in the full study protocol will be added to a secure master list, maintained in Dacima. All data will be retained in accordance with the Records Control Schedule.

View: 10.0.0 Data Security and Privacy: Data Types Storing

10.0 Data Types Collecting and Storing

1.0

Click the add button (below) to open an entry form to indicate the types and/or sources of the data that will be collected/stored as part of the project.

Instructions: For each type/source of data that will be collected as part of the project, this includes screening data, click the add button to open an entry form that lists the types and/or sources of data. Select a source/type of the data that will be collected/stored. Then indicate what, if any, identifiers or sensitive information will be collected/stored from the source/type (None is an option). To add another source/type click "OK Add Another" button to open up a new entry form to repeat the process.

Example 1: You are collecting data from VA Medical records including names, last 4 of SSN, and addresses. Therefore, you would select "VA medical record data" as the source, and then select in the identifiers: "Name or any derivative of name, such as initials," "Social Security Numbers," and "Geographical subdivisions smaller than a State (street address, city, county, precinct, zip code, and their equivalent geocodes, except for the initial three digits of a zip code)" as the identifiers being collected.

Example 2: You are screening VA Medical Records and recording the information you use to screen (i.e.: names, last 4 of SSN, and addresses, etc.) Note: This information must be treated as a Source document, please select "Screening" as the source and then select the identifiers "Name or any derivative of name, such as initials," "Social Security Numbers,", as applicable.

Data Type/Source Collection Details Identifiers

View

VA medical record data (i.e., diagnoses, procedures, visits) via chart review

Urinalysis results, number/type/dates of treatment encounters and missed/cancelled appointments, medications, diagnoses, and other relevant data will be extracted from participant medical records. These data will be de-identified and entered into a secure research database. Identifiers will be present

in VA medical record data. However, only de-identified data will be collected and stored. Social Security Numbers

Name or any derivative of name such as initials

View

Other

Behavioral/Cognitive Performance Measures (Response Time and Accuracy, Etc.)

Response time and accuracy data will be recorded during computerized experimental paradigms. Participants will perform one or more computer-based tasks during which they will make behavioral responses to stimuli. A computer program will be used to record the timing and accuracy of responses. In addition, data on cognitive performance will be collected by hand (e.g., using pencil/paper/stop watch) during the SLUMS/MoCA and Brown Peterson/Auditory Consonant Trigrams memory task. These data will be collected under the supervision of study investigators during the experimental session. A timestamp with the session date will be included in data files generated by the task presentation software. Otherwise, data will only be identified by the Study ID. Elements of dates (except year, for example, date of birth, admission date, discharge date, date of death, date of procedures; and all ages over 89)

Device identifiers and serial numbers

View

Other

Electroencephalography Data

EEG data will be acquired by study personnel using a standard EEG system. These data will be collected under the supervision of study investigators during the experimental session. A timestamp with the session date will be included in data files generated by the task presentation software. Information about the EEG device may also be included in this file. Otherwise, data will only be identified by the Study ID. Elements of dates (except year, for example, date of birth, admission date, discharge date, date of death, date of procedures; and all ages over 89)

Device identifiers and serial numbers

View

Other

Eye Movement / Pupillometry Data

Eye movement and pupillometry data may also be acquired by study personnel using a standard eye tracking / pupillometry system. These data will be collected under the supervision of study investigators during the experimental session. A timestamp with the session date will be included in data files generated by the task presentation software. Information about the eye tracking / pupillometry device may also be included in this file. Otherwise, data will only be identified by the Study ID. Elements of

dates (except year, for example, date of birth, admission date, discharge date, date of death, date of procedures; and all ages over 89)

Device identifiers and serial numbers

View

Questionnaires/Surveys, paper

Participants will complete a demographic information sheet, including general information (age, race, sex, etc.), as well as several self report questionnaires - these forms will only be identified by the participant's study ID. None

View

Other

For participants who enroll in the optional Goldstein substudy (Substudy 2), heart rate and activity monitoring (e.g., accelerometer-based physical activity and sleep metrics, ambient light, device wear-time) data will be recorded using an ActiGraph wGT3X-GT and paired Polar H7 heart rate monitor.

Data will be collected using wearable devices worn by participants (i.e., ActiGraph wGT3X-GT and paired Polar H7 heart rate monitor). Data collected by both the ActiGraph wGT3X-GT and Polar H7 heart rate monitor will be temporarily stored on the ActiGraph wGT3X-GT device during the two week recording interval. Data will subsequently be downloaded using TRM-approved ActiLife software. Data will generally be downloaded to a VA computer that is not connected to the VA network due to the need for a USB-based connection between the computer and the ActiGraph wGT3X-GT device. This computer is located in the PI's locked lab space in Building 30. Data will subsequently be transferred to the secure network drive for this study (behind the VA firewall) for storage. Elements of dates (except year, for example, date of birth, admission date, discharge date, date of death, date of procedures; and all ages over 89)

Device identifiers and serial numbers

View

Drug or alcohol abuse information

These data will be collected during interview procedures and will only be identified by the participant's study ID number in records maintained for the study. Patients will also be asked to report information including dates of recent substance use and prize preferences in the course of Contingency Management treatment sessions and this information will be recorded on CM session tracking forms; however, these forms will not include any identifying information. Specific information provided by self-report during CM treatment sessions may also be entered in the patient's chart based on guidelines for documenting CM treatment encounters, established by the VA CM National Implementation team. None

View

Interviews/focus groups

Participants will complete clinical/diagnostic interviews, as well as an interview about upcoming life events and the timeline follow-back procedure (a short interview addressing recent substance use). Notes will be taken regarding patient responses but will not include any identifying information. An audio-recording of interview procedures will not be made. Patients will also be asked to report information including dates of recent substance use and prize preferences in the course of Contingency Management treatment sessions and this information will be recorded on CM session tracking forms; however, these forms will not include any identifying information. Specific information provided by self-report during CM treatment sessions may also be entered in the patient's chart based on guidelines for documenting CM treatment encounters, established by the VA CM National Implementation team. None

View: 10.0.1 Data Security and Privacy: Social Security Numbers

10.0.1 Data Security and Privacy: Social Security Numbers

1.0 You indicated that you will be using all or some part of the research subjects' SSNs as part of this study. Which of the following will you be using:

Real Social Security numbers * **Yes** No

Scrambled Social Security numbers * Yes No

Last 4 digits of Social Security Number * **Yes** No

Other (some derivation of the SSN) * Yes No

If other, please explain:

2.0 * Please describe how subjects' Social Security numbers will be used in this study:

Subjects will be asked to provide their last name and the last four digits of the SSN in order to identify medical records for review during the telephone screening process. This information will be maintained in screening records, as per VA requirements. The last four digits of the SSN may also be used when accessing medical records for chart review after participants have provided written HIPAA authorization. In addition, specific study-related documentation including informed consent forms, HIPAA authorizations forms, and study payment forms may require that full SSN or last four SSN information be included for administrative and/or oversight purposes.

3.0 * Please describe the security measures that will be taken to protect SSNs.

The minimum necessary information related to the SSN (i.e., the last four digits) will be stored in a password protected database (powered by Dacima Clinical Suite) that will be maintained behind the VA firewall on a secure server, only accessible to study personnel. All paper documents including full or

partial SSN information will be stored in a locked filing cabinet on a secure floor of Building 30 and/or inside a locked office.

View: 10.1.0 Data Security and Privacy: Incoming Data

10.1.0 Incoming Data

1.0

* Will data be transferred into VAPHS?

No. Data is not being transferred into this facility

View: 10.2.0 Data Security and Privacy: Outgoing Data

10.2.0 Outgoing Data

1.0

* Will any of the data being collected/stored be transferred outside of VAPHS?

Yes. The data will be transferred outside of VAPHS, but will remain within the VA.

View: 10.3.0 Data Security and Privacy: Local Data Storage Types

10.3.0 Local Data Storage Types

1.0

* How will data be stored on this project? (Select all that apply)

On Paper X

Electronically X

View: 10.3.1 Data Security and Privacy: Local Data Storage Types - Paper

10.3.1 Local Data Storage Types - Paper

1.0

* All VA research data collected in paper must be stored in a locked room at VAPHS.

List the room number(s) and the campus(es) where data will be stored in the text box below.

Paper data will be stored at the VAPHS University Drive Campus in Building 30. Data will either be stored in a locked filing cabinet within a locked room (GA-136) or in a locked filing cabinet on a secure floor of Building 30 (Cubicle 1-12 and/or Office 1A-130). Files related to CM treatment sessions may additionally be stored with CM supplies in a locked filing cabinet in a secure room within a secure area in Building 29 or secure office used for CM treatment sessions within Building 30.

View: 10.3.2 Data Security and Privacy: Local Data Storage Types - Electronic

10.3.2 Local Data Storage Types - Electronic

1.0

* Where is the electronic data being stored? Select all that apply.

VAPHS Network (shared drive)
VAPHS Encrypted laptop
VA Encrypted VA external drive or thumb drive
VA Encrypted CD/DVD
CPRS
Other

If "Other" please describe OR if you would like to provide additional information for clarification, please elaborate in the text box below.
Dacima Clinical Suite will be used for database management, participant tracking, and randomization. Dacima Clinical Suite is a web-based Electronic Data Capture (EDC) software that allows setup and configuration of research study databases. The Dacima Clinical Suite has been approved for the intended use in the Technical Reference Manual (https://www.oit.va.gov/Services/TRM/ToolPage.aspx?tid=9433&tab=2) and has also been reviewed and approved for the intended use by VAPHS Privacy and Information Security Officers.

The software is designed to be very flexible so it can be used for different types of study designs including: Randomized Clinical Trial, Observational studies (Cohort, Case-Control, Cross-sectional), patient registries, web surveys, electronic Patient Report Outcomes (ePRO), Patient diaries and administrative databases. Dacima uses a SQL Server database (backend) to store meta data and study data, and a web interface (front end) that was developed with Microsoft .Net (C#), html, and Java Script. Wireless transmission is not allowed. Secure SSL connection ensures that all data sent between the browsers and the web servers is encrypted based on the SSL protocol. Only the data entered by the user in the browser is sent to the servers.

The software is housed on a virtual server provided and maintained by the VA at the VA Pittsburgh Healthcare System, Heinz Campus, Building 32, Room BA120. The software is compliant with FDA 21 CFR Part 11 requirements and includes a complete and comprehensive audit trail. It requires use of SSL/TLS certificates, and allows critical and routine OS and system security patches per VA requirements.

Use of the DACIMA software program requires user authentication with a strong user password, and the software has an auto logoff/lock program. The DACIMA software program will be accessed directly and the data will be stored on the VAPHS server. The data are backed up nightly in accordance with VAPHS protocol. Installation or updates to the software program require IT administrator privileges.

Deidentified electronic data from EEG recording sessions may additionally be backed-up (i.e., archived) using unencrypted CD/DVD storage which will be maintained inside a locked filing cabinet in a locked office location (GA-136) or in a cubicle on a secure floor of Building 30 (Cubicle 1-12 or Office 1A-130).

Examples of Dacima forms used for data entry are included under Section 15 (Miscellaneous Documents). It is noted that study personnel will enter all data into Dacima and that participants will not directly interact with Dacima in any way.

Additional Information:

A VAPHS encrypted laptop may be used in the acquisition of behavioral and/or EEG data in the current study. While the intention is not to permanently store these data on the encrypted laptop, they may be maintained there prior to transfer to the designated VA Network drive for storage. We additionally anticipate that machines used for acquisition of behavioral and EEG data may be disconnected from the VA network (i.e., not connected to the internet) in order to ensure accurate timing of stimuli in behavioral paradigms and event markers in EEG data acquisitions. Consequently, we may use a VA encrypted thumb drive or an encrypted CD/DVD to transfer data to the VA Network Drive. Once again, the intention will not be to permanently store these data on encrypted portable media. Files will be deleted and/or CD/DVD discs will be destroyed (using approved methods) following confirmation that files have been successfully transferred and that a back-up version of raw EEG data files has been successfully created. Importantly, these behavioral and EEG data files will not include any direct personal identifiers. As already noted, raw EEG data files will be backed up using CD/DVDs (either encrypted or unencrypted) and will be maintained in a locked filing cabinet on a secure floor of Building 30.

If you selected VAPHS or VA Network (Shared Drive), please provide the name of the drive (i.e. "MySharedDriveName (\\vapthshsare) (X:)"):

\\PTH_Groups\PRO2689WRAP

View: 10.4.0 Data Security and Privacy: Reusing Data

10.4.0 Data Security and Privacy: Reusing Data

1.0

* Will the data collected in this study be reused in other studies? Yes No

If yes, please describe where the data to be reused will be stored and how access to that data will be provided and monitored:

There is currently no plan to reuse the data collected in this study for other studies. However, per our DMAP, we must ensure that a de-identified version of the dataset will ultimately be made available to the public. Per our DMAP, de-identified, anonymized data will be made available to the public through government-approved mechanisms for dissemination such as the NIMH Data Archive. Preparation of de-identified, anonymized datasets will be conducted in consultation with VA Privacy and Security Officers. VA Privacy Officers will review all datasets prior to dissemination in order to verify that all personally-identifiable information has been removed. ORD guidance on specific data sharing requests will be consulted, if necessary. It is acknowledged that removal of PII/PHI may lead to additional restriction of shared information. Subject identifiers will only be accessible to authorized staff and will be securely maintained behind the VA firewall.

2.0

If this research is part of a grant, please upload the Data Management Access Plan (DMAP) or Resource Sharing Plan for this study.

Name Modified Date

DMAP 8/15/2018 2:53 PM

View: 10.5.0 Data Security and Privacy: Off-Site Storage and Transfer of Data

10.5.0 Off-Site Storage and Transfer of Data

1.0 * You indicated that data collected as part of this study will be transferred outside of VA/VAPHS. Please provide a justification for why the data must be stored, transmitted, and/or transferred off-site:

The current project will be conducted as part of the PI's Career Development Award. Dr. Siegle will serve as a mentor to the PI during the funding period and will provide critical guidance with respect to data quality optimization, selection and execution of data preprocessing and analytic techniques, as well as result interpretation and dissemination.

Click here for Research Data Security and Privacy Frequently Asked Questions

Specify in detail how data will be collected, entered, and analyzed. For multisite studies, if no data entry and/or analysis will occur on site, this should be specified. Specify how long each phase of the study will take to complete and provide a time line for each aspect of the study ending with the final analyses and projected publication/presentation timeframe. If you are seeking exempt status on the basis of

retrospective medical records review, please include the start and end dates (dates of creation) of the medical records you wish to use (Note: In order for the study to be granted exempt status the data must have already been collected prior to the date of submission of the application for exempt status) Also, provide all data entry forms or a complete list of the variables you will be collecting.

2.0 Please list all locations or individuals who will receive/be provided with the data, including sponsor, site monitors, coordinating center, University of Pittsburgh, non-VA investigators/collaborators, reading centers, core laboratories, other research laboratories, data monitoring committee, etc.

* Data Recipients and Identifiers:

Recipient and Description

Identifier Identifier Description Transfer Methods

University of Pittsburgh

Greg Siegle, PhD, Associate Professor of Psychiatry and Psychology University of Pittsburgh Western Psychiatric Institute and Clinic 3811 O'Hara Street Pittsburgh, PA 15213 gsiegle@pitt.edu

None De-identified, aggregate data (such as group averages of behavioral, EEG, or self-report data)

Electronic file transfer

Other (list below)

Hard copy transfer via mail or from person-to-person.

Any identifiable information that is being shared with these individuals/entities must be described in the HIPAA authorization (in the disclosure section).

View: 10.5.1 Data Security and Privacy: Keeping a Copy of the Data

10.5.1 Data Security and Privacy: Keeping a Copy of the Data

1.0

* How will the study team keep a copy of the data at VAPHS that is being transferred?

CPRS (source data)
Paper (copies of CRFs, questionnaires, etc.)
Other (specify)

Specify other method of maintaining a copy of the data being transferred:

All primary data (source data, paper data, and raw electronic data files) will be maintained at VAPHS. Only copies (either electronic or hard copy) of de-identified aggregate data (for example, plots depicting single subject or group average data) will be transferred to recipients outside of VAPHS.

2.0 * Upload the VA Data Storage and Retrieval Worksheet:

VA Data Storage Placeholder(0.01)

View: 10.6.0 Data Security and Privacy: HIPAA

10.6.0 Data Security and Privacy: HIPAA

The Healthcare Insurance Portability and Accountability Act (HIPAA) prohibits the use of a person's Protected Health Information without a valid authorization.

1.0

* Select the option which fits this study:

Not applicable: No PHI is being used or disclosed by VAPHS

Not applicable: Waiver has been requested

HIPAA Authorization (Combined Consent and HIPAA Authorization)

HIPAA Authorization (Standalone)

Upload HIPAA authorization (Standalone) here:

Document Modified Date Version Number

View HIPAA Placeholder(0.02) 8/13/2019 3:15 PM 0.02

2.0

At screening will clinical personnel be asked to share potential participants PHI:

Yes **No**

If yes, please upload the 10-5345:

View: 10.7.0 Data Security and Privacy: Additional Information

10.7.0 Data Security and Privacy: Additional Information

1.0

Does this research involve...

* ...specially obtained software? **Yes** No

If yes, please describe the software and what it is being used for:

Specialty software will be used for the presentation of experimental stimuli (e.g., STIM, E-Prime, and/or other presentation program TBD), acquisition of EEG data (SCAN and/or other acquisition program), analysis of EEG data (SCAN, EEGlab, and/or other analysis program TBD), and acquisition/analysis of eye tracking and/or pupillometry data (acquisition/analysis program TBD). ActiLife software will additionally be used to download and analyze activity and heart rate data for Substudy 2. Only TRM-approved software will be used.

* ...one or more Web-based applications? **Yes** No

If yes, please describe the application and what it is being used for:

Dacima Clinical Suite is a web-based Electronic Data Capture (EDC) software that allows setup and configuration of research study databases. The software is designed to be very flexible so it can be used for different types of study designs including: Randomized Clinical Trial, Observational studies (Cohort, Case-Control, Cross-sectional), patient registries, web surveys, electronic Patient Report Outcomes (ePRO), Patient diaries and administrative databases. Dacima uses a SQL Server database (backend) to

store meta data and study data, and a web interface (front end) that was developed with Microsoft .Net (C#), html, and Java Script. Wireless transmission is not allowed. Secure SSL connection ensures that all data sent between the browsers and the web servers is encrypted based on the SSL protocol. Only the data entered by the user in the browser is sent to the servers.

The software is housed on a virtual server provided and maintained by the VA at the VA Pittsburgh Healthcare System, Heinz Campus, Building 32, Room BA120. The software is compliant with FDA 21 CFR Part 11 requirements and includes a complete and comprehensive audit trail. It requires use of SSL/TLS certificates, and allows critical and routine OS and system security patches per VA requirements.

Use of the DACIMA software program requires user authentication with a strong user password, and the software has an auto logoff/lock program. The DACIMA software program will be access directly and the data will be stored on the VAPHS server. The data are backed up nightly in accordance with VAPHS protocol. Installation or updates to the software program require IT administrator privileges.

VA Video Connect (or other VA-approved telehealth technology, if available) may also be used to remotely interact with research participants via video call.

* ...mobile devices? **Yes** No

If yes, please describe:

A research-grade wearable activity monitor (wGT3X-BT) and heart rate monitor (Polar H7) will be used in the context of optional Substudy 2. Data collected by both devices will be logged to the wGT3X-BT. Data stored on this device cannot be directly accessed through the device and will not be transmitted over the internet. Data will be downloaded from the device via USB using ActiLife software on a VA machine on VA property.

2.0

* Will a Certificate of Confidentiality be obtained for this study? Yes No

If yes, please attach the Certificate of Confidentiality:

3.0

* Will VA sensitive information be transported and utilized outside protected environments? Yes No

If you answered yes above, please upload a fully executed VAPHS Memo to Take VA Sensitive Information Outside a Protected Environment by following these instructions .

View: 10.8.0 Data Security and Privacy: Certifications

10.8.0 Certifications

1.0 * I certify that all study staff are up-to-date and will remain up-to-date with Information Security Awareness Training, Rules of Behavior, and VHA Privacy Training. **Yes** No

2.0 * I also certify that when an individual is no longer part of the study team, access will be removed to research study data. **Yes** No

3.0 * I certify that all research records will be maintained in accordance with the Veterans Health Administration (VHA)Records Control Schedule. Paper records will be disposed of using methods deemed appropriate by the VAPHS Privacy Officer, and all electronic data will be sanitized using methods rendered appropriate by the VAPHS ISO. **Yes** No

4.0 * I certify that any loss or compromise of any VA sensitive information (including research data), VA equipment or device, or any non-VA equipment or device that is used to transport, access, or store VA information will be reported in accordance with the reporting requirements outlined in VA Handbook 6500. **Yes** No

5.0 * I certify that, in accordance with VA Handbook 6500, no personal laptops will be used for official VA business in conjunction with this study. **Yes** No

View: 11 Local Data Safety Monitoring Plan

Local Data Safety Monitoring Plan

For local studies, a data and safety monitoring plan (DSMP) must be established.

1.0 * Please describe how the study procedures and data being collected will be continuously monitored so that changes in the risk/benefit ratio can be determined in a timely fashion during the course of the study:

Our data and safety-monitoring plan will be implemented to ensure that there are no changes in the benefit/risk ratio during the study and that confidentiality of research data is maintained. Human Subjects safety training for all personnel is required. Upon learning of any adverse events, we shall report such events as soon as possible and within IRB guidelines using the standard forms and/or procedures set forth by the VA Pittsburgh IRB regulations. The biannual renewal for this study will also serve as the update of the data safety-monitoring plan. The Principal Investigator holds the role of Study Monitor and is responsible for implementation and performance of the Data Safety Monitoring Plan.

2.0 * Describe how frequently Investigators, study personnel, and the clinical coordinators involved in the study will meet and/or review study data.

Investigators, study personnel, and study coordinators involved in the study meet a minimum of four times per year (quarterly) to discuss the study (e.g., study goals, progress, modifications, documentation, adverse events, protocol deviations) and address any issues or concerns at this time. The Principal Investigator or her designee oversees these meetings.

3.0 * Will this study use a Data Safety Monitoring Board or Data Monitoring committee?

Yes No

4.0 * Will this study use a Medical Monitor?

Yes **No**

View: 11.1 Data Safety Monitoring Board/ Data Monitoring Committee

Data Safety Monitoring Board/ Data Monitoring Committee

1.0 * List the affiliations and qualifications of those monitors who are not associated with the study or describe the composition of the DSMB:

The current study has been assigned to the CSR&D Data Monitoring Committee (DMC). This DMC committee is made up of the following members

Steven D. Forman, M.D., Ph.D.
Chair of DMC/Recused
Moderates meetings for both initial review and ongoing study reports

David Smelson, Psy.D.
Voting member
Primary Reviewer of protocol and ongoing reports

Denise May Sloan, Ph.D.
Voting Member
Secondary Reviewer for protocol and ongoing reports

Ping Luo, Ph.D.
Voting Member
Biostatistical Reviewer for protocol and ongoing reports

2.0 * Describe how frequently the independent monitor(s) or DSMB will meet and/or review study data:

The DMC has conducted a pre-review and initial review prior to the start of data collection; the date of the initial review was 2/28/19. Following the start of recruitment, meetings to review study data will subsequently occur every 4 months.

3.0 * Describe the type of data (e.g., blinded or unblinded) to which the independent monitor(s) or DSMB will have access:

The DMC will have access to unblinded data.

4.0 Document that minutes will be kept.

The DMC will keep meeting minutes. Any meeting minutes and/or reports provided by the DMC will be uploaded on an annual basis at the time of Continuing Review.

5.0 * Please upload the DSMB/DMC Charter:

DMC Charter(0.03)

View: 12 Costs and Payments

Costs and Payments

1.0 * Does this study have a budget?:

Yes No

If yes, please upload the current budget:

CDA Budget(0.01)

2.0

* Will patients receive payments for this study?

Yes No

If yes, please upload the financial letter of support (either from the Business Service line or the Veterans Health Foundation) or documentation waiving the requirement of a letter of support:

Financial Letter of Support 0.03

VHF Letter of Support (Substudy 2) 0.01

3.0

* Are you paying patients using the WePay system?

no

View: 12.1 Costs

Costs

1.0 * Will subjects be required to pay for any services outside of the VHA that may be required as part of participating in this research study?

No, participants will not be required to pay for services and procedures outside the VHA as part of this study.

View: 12.2 Participant Payments

Participant Payments

1.0 * Please explain how the proposed payments are reasonable and commensurate with the expected contributions of the subject:

Payment for study visits will help to cover the cost of time and effort by study participants.

A payment of $5-10 will be provided for short visits related to the study (e.g., Weekly and Monthly Check-in visits), lasting 5-30 minutes in duration. It may be possible to conduct Check-in appointments by phone in some cases. However, we would prefer that participants attend appointments in person and must provide an adequate payment to ensure that this is an option for all individuals involved in the study. Due to the necessity of longitudinal data collection, we would also like to incentivize study completion by offering a $10 completion bonus to participants who complete their final study contact. Longer study appointments (Screening , Baseline Assessment, and Follow-Up assessment) will take 2.5-4 hours to complete and therefore warrant increased compensation for time spent completing study procedures. We will therefore provide $20 for completion of the Screening visit and $35 for completion of Baseline and Follow-Up Assessments.

We will also provide performance based bonus payments of $12-25 to encourage naturalistic responses during one or more cognitive-behavioral tasks involving responses to hypothetical reward. This performance-based bonus will generally be paid out at the time of Baseline and Follow-Up Assessment. During a modified Monetary Incentive Delay task, participants will earn points based on their responses and these points will be translated into a monetary bonus after the task is complete. Responses during our personalized delay discounting task may additionally be factored in when determining the specific amount and timing of this monetary bonus in order to encourage naturalistic decision-making during the delay discounting task. Performance-based bonus amounts have been determined such that they are similar to prizes routinely won in the context of Contingency Management.

Participants in Substudy 2 will additionally be eligible to receive a payment of $40 to compensate them for time, effort, and inconvenience related to engaging in remote activity and heart rate monitoring over the first two weeks of treatment.

2.0 * Please provide information on how the subject payments are fair and appropriate, and that they do not constitute (or appear to constitute) undue pressure or influence on the prospective research subjects to volunteer for, or to continue to participate in, the research study. In additional the payments do not constitute (or appear to constitute) coercion to participate in, or continue to participate in, the research study:

A performance-based bonus of $12-25 will be provided based performance during our modified monetary incentive delay task and/or our personalized delay discounting task. The amount and/or timing of this bonus will be determined on the basis of participant responses during computerized cognitive tasks. In effect, we do not anticipate that this payment will directly bear on any participant's decision to participate as the amount and timing of the payment will be unknown at the time of informed consent. Participants will be informed that they will receive this payment (even if provided at some delay after the assessment) regardless of continued participation in the study.

A payment of $40 is also considered to be a fair and appropriate for remote monitoring activities. Remote monitoring will require low effort on the part of the participant but will represent a daily inconvenience over a two week period.

3.0 * Specify the amount, form of payment and the specific disbursement schedule of payments:

For participating in the study explanation/consent review session and pre-assessment screening and testing procedures (Screening Visit), participants will be authorized for $20 (via EFT) to compensate them for time and effort. After the enrollment and assessment procedures (Baseline Assessment), participants will be authorized for an additional $35 (via EFT) to compensate them for time and effort during that session. After each weekly check-in visit during the 12 Week Treatment Interval, participants will be authorized for an additional $5 to compensate them for the time and effort spent on the study. Participants will generally be asked to complete a Follow-Up Assessment at the 12 week timepoint and will receive a payment of $35 to compensate them for time and effort during that visit. Under circumstances that a Follow-Up Visit cannot be conducted and a standard Check-in Visit occurs instead, the participant will be compensated $5. Participants assigned to VoucherPBCM or TangiblePBCM conditions will additionally be asked to participate in monthly check-in visits for 6 months after treatment and will receive $10 for each of these assessments. All participants will be eligible for a completion bonus of $10 at the time of their last study contact (i.e., 6 Month Post-Treatment Check-In for CM participants). In addition to regular study payments, participants will also receive a performance-based bonus from tasks completed at Baseline and Follow-up Sessions. The amount and/or timing of this bonus payment will be determined by task performance. Performance-based bonuses are frequently used to improve motivation and naturalistic responses in human subjects research involving reward processing. The average performance-based bonus payment will be $20 (range = $12-25) at both Baseline and Follow-Up. Taken together, full participation in the study will result in an average total payment of $260 over 9 months for CM-assigned Veterans (range: $250-$270).

Participants in Substudy 2 will receive a single $40 payment via Greenphire ClinCard at the conclusion of the two week monitoring period.

For Healthy Controls:

For participating in the screening visit (informed consent, cognitive screening and interviews, questionnaires, activity monitoring procedures), baseline assessment (breathalyzer, urine and/or oral saliva drug screens, cognitive-behavioral tasks, EEG procedures) and the follow-up visit, participants will be authorized $20 for the screening visit, $50-60 for the Baseline assessment, $50-60 for the Follow-up assessment, and $40 for participation in activity monitoring. Taken together, full participation in the study will result in a total payment of $160-$180.

4.0 * Are the subjects being paid employees?

yes

If yes, please describe how it will be in accordance with the SOP:

It is possible that a participant in the study may also be a paid VA employee. In such cases the participant will be informed that he or she may not participate in any study activities for which he/she may be compensated during his/her VA tour of duty.

View: 14 References

References:

1.0

* Please provide a list of references (Multi-site protocols: You may reference the page numbers in the original protocol):

References

1. Wagner, T, Harris, K, Federman, B, et al., Prevalence of substance use disorders among veterans and comparable nonveterans from the National Survey on Drug Use and Health.Psychol Serv, 2007.4: p.149-57.
2. Lan, C., Fiellin, D., Barry, D., et al., The epidemiology of substance use disorders in US Veterans: A systematic review and analysis of assessment methods. Am J Addict, 2016. 25:7-24.
3. Tsai, J & R Rosenheck, Risk factors for homelessness among US veterans. Epidemiol Rev, 2015. 37: p.177-95.
4. Trivedi, R., Post, E., Sun, H., et al., Prevalence, Comorbidity, and Prognosis of Mental Health Among US Veterans. Am J Public Health, 2015. 105: p.2564-9.
5. Erickson, S., Rosenheck, R., Trestman, R. et al., Risk of incarceration between cohorts of veterans with and without mental illness discharged from inpatient units. Psychiatr Serv, 2008. 59: p.178-83.
6. Vazan, P., A. Golub, & A. Bennett, Substance use and other mental health disorders among veterans returning to the inner city: prevalence, correlates, and rates of unmet treatment need. Subst Use Misuse, 2013. 48: p.880-93.
7. el-Serag, H., Kunik, M., Richardson, P., et al., Psychiatric disorders among veterans with hepatitis C infection. Gastroenterology, 2002. 123: p.476-82.

8. Roux, P., Lions, C., Vilotitch, A., et al., Correlates of cocaine use during methadone treatment: implications for screening and clinical management (ANRS Methaville study). Harm Reduct J, 2016.13: p.12.
9. Hien, D.A., et al., Posttraumatic stress disorder and short-term outcome in early methadone treatment. J Subst Abuse Treat, 2000. 19: p. 31-7.
10. Manhapra, A, E Stefanovics, & R Rosenheck, Treatment outcomes for veterans with PTSD and substance use: Impact of specific substances and achievement of abstinence. Drug Alcohol Depend, 2015.156:p.70-7.
11. Dixon, L., Dual diagnosis of substance abuse in schizophrenia: prevalence and impact on outcomes. Schizophr Res, 1999. 35 Suppl: p.S93-100.
12. Bombardier, C., Fann, J., Temkin, N., et al., Rates of major depressive disorder and clinical outcomes following traumatic brain injury. JAMA, 2010. 303: p.1938-45.
13. Schoenhard, W,Dept of VA memorandum: Evidence based treatment for substance use disorders, 2/23/11.
14. Petry, N., DePhilippis, D., Rash, C., et al., Nationwide dissemination of contingency management: the Veterans Administration initiative. Am J Addict, 2014. 23: p.205-10.
15. Petry, N., Tedford, J., Austin, M., et al., Prize reinforcement contingency management for treating cocaine users: how low can we go, and with whom? Addiction, 2004. 99: p.349-60.
16. Benishek, L., Dugosh, K., Kirby, K., et al., Prize-based contingency management for the treatment of substance abusers: a meta-analysis. Addiction, 2014. 109: p.1426-36.
17. Petry, N., Barry, D., Alessi, S., et al., A randomized trial adapting contingency management targets based on initial abstinence status of cocaine-dependent patients. J Consult Clin Psychol, 2012. 80: p.276-85.
18. Regier, P. & A. Redish, Contingency Management and Deliberative Decision-Making Processes. Front Psychiatry, 2015. 6: p.76.
19. Bickel, W., Snyder, S., Quisenberry, A., et al., Competing neurobehavioral decision systems theory of cocaine addiction: From mechanisms to therapeutic opportunities. Prog Brain Res, 2016. 223: p.269-93.
20. SAMHSA, Results from the 2011 National Survey on Drug Use and Health: Summary of National Findings. (HHS Publication No. (SMA) 12-4713). Rockville, MD., 2012.
21. Chang, G., Martin, K., Tang, M., et al., Inpatient hospitalization for substance use disorders one year after residential rehabilitation: predictors among US veterans. Am J Drug Alcohol Abuse, 2015: p.1-7.
22. Golub, A., Vazan, P., Bennett, A., et al., Unmet need for treatment of substance use disorders and serious psychological distress among veterans: a nationwide analysis using the NSDUH.Mil Med,2013.178:107-14.
23. Wagner, T., P. Sinnott, & A. Siroka, Mental health and substance use disorder spending in the Department of Veterans Affairs, fiscal years 2000-2007. Psychiatr Serv, 2011. 62: p.389-95.
24. Oliva, E., Trafton, J., Harris, A., et al., Trends in opioid agonist therapy in the Veterans Health Administration: is supply keeping up with demand? Am J Drug Alcohol Abuse, 2013. 39: p.103-7.
25. Heyman, G., Quitting drugs: quantitative and qualitative features. Annu Rev Clin Psychol, 2013. 9: p.29-59.
26. Vocci, F., Can replacement therapy work in the treatment of cocaine dependence? And what are we replacing anyway? Addiction, 2007. 102: p.1888-9.
27. Higgins, S., Budney, A., Bickel, W., et al., Incentives improve outcome in outpatient behavioral treatment of cocaine dependence. Arch Gen Psychiatry, 1994. 51: p.568-76.

28. Petry, N., Pierce, J., Stitzer, M., et al., Effect of prize-based incentives on outcomes in stimulant abusers in outpatient psychosocial treatment programs: a national drug abuse treatment clinical trials network study. Arch Gen Psychiatry, 2005. 62: p.1148-56.
29. Prendergast, M., Podus, D., Finney, J., et al., Contingency management for treatment of substance use disorders: a meta-analysis. Addiction, 2006. 101: p.1546-60.
30. Lussier, J., Heil, S., Mongeon, J., et al., A meta-analysis of voucher-based reinforcement therapy for substance use disorders. Addiction, 2006. 101: p.192-203.
31. Stitzer, M. & G. Bigelow, Contingent reinforcement for carbon monoxide reduction: within-subject effects of pay amount. J Appl Behav Anal, 1984. 17: p.477-83.
32. Silverman, K., Wong, C., Higgins, S., et al., Increasing opiate abstinence through voucher-based reinforcement therapy. Drug Alcohol Depend, 1996. 41: p.157-65.
33. Petry, N., Martin, B., Cooney, J. et al., Give them prizes, and they will come: contingency management for treatment of alcohol dependence. J Consult Clin Psychol, 2000. 68: p.250-7.
34. Petry, N., Alessi, A., Marx, J., et al., Vouchers versus prizes: contingency management treatment of substance abusers in community settings. J Consult Clin Psychol, 2005. 73: p. 1005-14.
35. Schmitz, J., Green, C., Stotts, A., et al., A two-phased screening paradigm for evaluating candidate medications for cocaine cessation or relapse prevention: modafinil, levodopa-carbidopa, naltrexone. Drug Alcohol Depend, 2014. 136: p.100-7.
36. Hagedorn, H., Noorbaloochi, S., Simon, A., et al., Rewarding early abstinence in Veterans Health Administration addiction clinics. J Subst Abuse Treat, 2013. 45: p.109-17.
37. Ghitza, U., Epstein, D., Schmittner, J., et al., Effect of reinforcement probability and prize size on cocaine and heroin abstinence in prize-based contingency management. J Appl Behav Anal, 2008. 41: p.539-49.
38. Ahmed, S., Validation crisis in animal models of drug addiction: beyond non-disordered drug use toward drug addiction. Neurosci Biobehav Rev, 2010. 35: p.172-84.
39. Bigelow, G., R. Griffiths, & I. Liebson, Experimental models for the modification of human drug self-administration: Methodological developments in the study of ethanol self-administration by alcoholics. Fed
Proc, 1975. 34: p.1785-92.
40. Yi, R., Stuppy-Sullivan, A., Pickover, A., et al., Impact of construal level manipulations on delay discounting. PLoS One, 2017. 12: p. e0177240.
41. Washio, Y., Higgins, S., Heil, S., et al., Delay discounting is associated with treatment response among cocaine-dependent outpatients. Exp Clin Psychopharmacol, 2011. 19: p.243-8.
42. Ling Murtaugh, K., Krishnamurti, T., Davis, A., et al., Spend today, clean tomorrow: predicting methamphetamine abstinence in a randomized controlled trial. Health Psychol, 2013. 32: p.958-66.
43. Aharonovich, E., Hasin, D., Brooks, A., et al., Cognitive deficits predict low treatment retention in cocaine
dependent patients. Drug Alcohol Depend, 2006. 81: p.313-22.
44. Aharonovich, E., E. Nunes, & D. Hasin, Cognitive impairment, retention and abstinence among cocaine
abusers in cognitive-behavioral treatment. Drug Alcohol Depend, 2003. 71: p.207-11.
45. Dean, A., London, E., Sugar, C., et al., Predicting adherence to treatment for methamphetamine dependence from neuropsychological and drug use variables. Drug Alcohol Depend, 2009. 105: p.48-55.

46. Ledgerwood, D. & N. Petry, Rating contingency management sessions that reinforce abstinence using the
Contingency Management Competence Scale, U.o.C.H. Center, Editor. 2010.
47. Rass, O., Schacht, R., Buckheit, K., et al., A randomized controlled trial of the effects of working memory
training in methadone maintenance patients. Drug Alcohol Depend, 2015. 156: p.38-46.
48. Bickel, W., Li, R., Landes, R., et al., Remember the future: working memory training decreases delay discounting among stimulant addicts. Biol Psychiatry, 2011. 69: p.260-5.
49. Balodis, I., Kober, H, Worhunsky, P., et al., Neurofunctional Reward Processing Changes in Cocaine Dependence During Recovery. Neuropsychopharmacology, 2016. 41: p.2112-21.
50. Prause, N., Siegle, G., Deblieck, C., et al., EEG to Primary Rewards: Predictive Utility and Malleability by
Brain Stimulation. PLoS One, 2016. 11: p.e0165646.
51. Simon, J., Skunde, M., Wu., M., et al., Neural dissociation of food- and money-related reward processing
using an abstract incentive delay task. Soc Cogn Affect Neurosci, 2015. 10: p.1113-20.
52. Forster, S., Carter, C., Cohen, J., et al., Parametric manipulation of the conflict signal and control-state
adaptation. J Cogn Neurosci, 2011. 23: p.923-35.
53. Fedota, J., Matous, A., Salmeron, B., et al., Insula Demonstrates a Non-Linear Response to Varying Demand for Cognitive Control and Weaker Resting Connectivity With the Executive Control Network in Smokers. Neuropsychopharmacology, 2016. 41: p.2557-65.
54. Peters, J. & C. Buchel, Episodic future thinking reduces reward delay discounting through an enhancement
of prefrontal-mediotemporal interactions. Neuron, 2010. 66: p.138-48.
55. Finn, P., R. Gunn, & K. Gerst, The Effects of a Working Memory Load on Delay Discounting in Those with
Externalizing Psychopathology. Clin Psychol Sci, 2015. 3: p.202-214.
56. Raabe, A., Grusser, S., Wessa, M., et al., The assessment of craving: psychometric properties, factor structure and a revised version of the Alcohol Craving Questionnaire. Addiction, 2005. 100: p.227-34.
57. Zuckerman, M. & A. Aluja, Measures of Sensation Seeking, in Measures of Personality and Social Psychological Constructs, Boyle, Saklofske, & Matthews, Editors. 2015, Academic Press. p.352-380.
58. Stotts, A., Vujanovic, A., Heads, A., et al., The role of avoidance and inflexibility in characterizing response to contingency management for cocaine use disorders. Psychol Addict Behav, 2015. 29: p.408-13.
59. Miller, W. & J. Tonigan, Assessing drinkers' motivation for change: the Stages Of Change Readiness And
Treatment Eagerness Scale (SOCRATES). Psychology of Addictive Behaviors, 1996. 10: p.81-89.
60. Adinoff, B., Talmadge, C., Williams, M. et al., Time to Relapse Questionnaire (TRQ): a measure of sudden
relapse in substance dependence. Am J Drug Alcohol Abuse, 2010. 36: p.140-9.
61. Aluja, A. & A. Blanch, Neuropsychological Behavioral Inhibition System (BIS) and Behavioral Approach

System (BAS) assessment: a shortened Sensitivity to Punishment and Sensitivity to Reward Questionnaire
version (SPSRQ-20). J Pers Assess, 2011. 93: p.628-36.
62. Crawford, J., Smith, G., Maylor, E. et al., The Prospective and Retrospective Memory Questionnaire (PRMQ): Normative data and latent structure in a large non-clinical sample. Memory, 2003. 11: p.261-75.
63. Sklar, S., H. Annis, and N. Turner, Development and validation of the drug-taking confidence questionnaire: a measure of coping self-efficacy. Addict Behav, 1997. 22: p.655-70.
64. Strathman, A., Gleicher, F., Boninger, D. S., & Edwards, C. S. (1994). The consideration of future consequences: Weighing immediate and distant outcomes of behavior. Journal of Personality and Social Psychology, 66(4), 742-752. doi: 10.1037/0022-3514.66.4.742
65. Heatherton TF, Kozlowski LT, Frecker RC, Fagerström KO. The Fagerström Test for Nicotine Dependence: a revision of the Fagerström Tolerance Questionnaire. Br J Addict. 1991;86:1119–27.
66. Zarse, E., Neff, M., Yoder, R., et al. The adverse childhood experiences questionnaire: Two decades of research on childhood trauma as a primary cause of adult mental illness, addiction, and medical diseases. Cogent Medicine. 2019; 6: 1581447.
67. Shura, R., J. Rowland, & H. Miskey, Auditory Consonant Trigrams: A Psychometric Update. Arch Clin Neuropsychol, 2016. 31: p 47-57.
68. Petry, N. & M. Stitzer, Contingency Management: Using motivational incentives to improve drug abuse treatment. Psychotherapy Development Center Training Series 6, 2002, Yale U: New Haven, CT.
69. Gajewski, P., G. Freude, & M. Falkenstein, Cognitive Training Sustainably Improves Executive Functioning in Middle-Aged Industry Workers Assessed by Task Switching: A Randomized Controlled ERP Study. Front Hum Neurosci, 2017. 11: p. 81.
70. Horowitz-Kraus, T. & Z. Breznitz, Can the error detection mechanism benefit from training the working memory? A comparison between dyslexics and controls--an ERP study. PLoS One, 2009. 4: p.e7141.
71. Rash, C., Olmstead, T., Petry, N., Income does not affect response to contingency management treatments among community substance abuse seekers. Drug Alcohol Depend, 2009. 104: p.249-53.

View: 15 Miscellaneous Documents

Miscellaneous Documents

If you have any documents that need to be included in this submission, but do not fit in any of the previous sections please upload them here.

Document Description	Version Number
View Approved COVID Risk Assessment(0.01)	0.01
View Letter of Support - CTAD(0.01)	0.01
View Letter of Support - Lab and Ancillary Testing(0.01)	0.01

View Protocol For Cleaning EEG Caps(0.02) 0.02

View Remote Monitoring Handout - Substudy 2(0.01) 0.01

View: SF - Final Page

Final Page

You have completed your application!

Please hit "Finish" to save and exit the application. Doing so will NOT submit the application for review.

Please note that a submission may only be forwarded to the IRB by the Principal Investigator. To do this, the Principal Investigator must press the "SUBMIT STUDY" button in My Activities for this Study ID:Pro00002689.

You can track the ongoing status of your submission by logging into the study workspace.

Please feel free to contact the IRB with any questions or concerns.

View: Create/Edit

Study Funding Source

1.0 * Funding Source Name:

Clinical Science R&D

If you can't find the Funding Source above, choose "Other" and enter it here:

View: Create/Edit

Study Funding Source

1.0 * Funding Source Name:

View

If you can't find the Funding Source above, choose "Other" and enter it here:

Veterans Research Foundation of Pittsburgh (VRFP)

View: VA Create-Edit

* Device Name: acti32Champ EEG Acquisition System

* Use of Device: Investigational Device Not Yet Approved for use

Manufacturer: Brain Products GmbH

IDE Class:

IDE Number(if Applicable):

Risk Level Determined by Sponsor: Non-Significant Risk

Upload Device Brochure

actiCHamp Manual(0.01)

Provide any other notes about how this device will be used or justification for lack of IDE number

This is a nonmedical device that will be used for the acquisition of electroencephalography (EEG) data in accordance with manufacturer operating standards. This device is non-invasive and will only be used to monitor naturally-occurring biological signals and processes in vivo.

The actiCHamp is intended to be used for research applications only and is not sold, designed or intended to be used as medical devices as defined in EU Directive 93/42/EEC, nor is it intended to be

used for other medical applications such as diagnosis or treatment of disease. The actiCHamp hardware has been tested and certified as per the relevant EMC and electrical safety standards. A non-medical CE certificate is available on request.

This equipment was reviewed and approved for purchase by the VAPHS Bio Medical Review committee on 5/9/2019.

Is the investigator hold the IDE for this device?

Yes No

If yes please provide a basis for risk level.

View: VA Create-Edit

* Device Name: GT3XP-BTLE 4GB Activity Monitor

* Use of Device: FDA Approved Device used in approved manner

Manufacturer: Actigraph, LLC

IDE Class: Class II

IDE Number(if Applicable): n/a

Risk Level Determined by Sponsor: Non-Significant Risk

Upload Device Brochure

Actigraph Brochure(0.01)

Provide any other notes about how this device will be used or justification for lack of IDE number

GOLDSTEIN SUBSTUDY ONLY: This device will be used in accordance with manufacturer instructions. The device tracks physical activity, sleep, and heartrate data (logged from a linked Polar H7 device). ActiGraph activity monitors are FDA 510(k) cleared and ActiGraph is ISO-13485:2016 certified.

Is the investigator hold the IDE for this device?

Yes **No**

If yes please provide a basis for risk level.

View: VA Create-Edit

* Device Name: ISCAN model RK406 Infra-red Pupillometer
* Use of Device: FDA Approved Device used in approved manner

Manufacturer: ISCAN

IDE Class:

IDE Number(if Applicable): n/a

Risk Level Determined by Sponsor: Non-Significant Risk

Upload Device Brochure

ISCAN Website(0.01)

Provide any other notes about how this device will be used or justification for lack of IDE number

This is a Class I medical device that will be used in an approved manner to monitor eye movement, pupil dimensions, and blinks during the EEG procedure. This device is non-invasive and will only be used to monitor naturally-occurring biological signals and processes in vivo.

Is the investigator hold the IDE for this device?

Yes **No**

If yes please provide a basis for risk level.

View: VA Create-Edit

* Device Name: Polar H7
* Use of Device: FDA Approved Device used in approved manner

Manufacturer: Polar

IDE Class: Class II

IDE Number(if Applicable): n/a

Risk Level Determined by Sponsor: Non-Significant Risk

Upload Device Brochure

Polar H7 Info Sheet(0.01)

Provide any other notes about how this device will be used or justification for lack of IDE number

GOLDSTEIN SUBSTUDY ONLY: This device will be worn around the chest to remotely measure heart rate. These data are transmitted via Bluetooth to the linked ActiGraph device for storage. Polar fitness monitors have been provided FDA 510(k) clearance. The Polar H7 is currently marketed as a commercial device and will not be used to diagnose, treat, or prevent a medical condition.

Is the investigator hold the IDE for this device?

Yes **No**

If yes please provide a basis for risk level.

View: Risk Detail Entry

Address for each screening procedure, research intervention/interatction, and follow-up/monitoring procedure:

* Research Activity:

Activity / HR Monitoring (GOLDSTEIN SUBSTUDY ONLY)

Common Risks:

Infrequent Risks:

A mild allergic reaction (e.g., skin irritation) to the ActiGraph wrist strap or Polar HR chest strap is possible. Participants will be informed of this risk and asked to disclose known allergies to rubber or synthetic textiles during the informed consent process for Substudy 2. Participants will also be provided with a handout with instructions for reducing the risk of skin irritation, as well as discontinuing use and contacting the study team if irritation does occur.

Other Risks:

View: Risk Detail Entry

Address for each screening procedure, research intervention/interatction, and follow-up/monitoring procedure:

* Research Activity:

Confidentiality

Common Risks:

As private information is collected as part of this study, there is a risk of loss of privacy and confidentiality. This risk will be described during the informed consent procedure. In addition, all electronic and paper data will be stored in an approved, secure location and will not be transmitted outside the VA. All possible efforts will be made to limit the inclusion of personally identifiable information on study-related documents. Personally identifiable information may, however, appear in chart-based (i.e., CPRS) documentation generated in the course of clinical services administered through the study.

Infrequent Risks:

Other Risks:

View: Risk Detail Entry

Address for each screening procedure, research intervention/interatction, and follow-up/monitoring procedure:

* Research Activity:

Interviews

Common Risks:

There are no common risks associated with this procedure.

Infrequent Risks:

It is possible that participants could experience psychological distress due to questions during diagnostic or substance use assessments. However, participants will be informed that they can skip questions they do not wish to answer.

Other Risks:

View: Risk Detail Entry

Address for each screening procedure, research intervention/interatction, and follow-up/monitoring procedure:

* Research Activity:

EEG Recording

Common Risks:

There are no common risks associated with this procedure.

Infrequent Risks:

Infrequent Risks:

1. On rare occasions, participants may experience slight itchiness due to the conductive gel used at electrode sensor sites. This reaction occurs in less than 1% of people. Participants will be instructed to let study personnel know if they experience discomfort during the EEG procedure and may choose to stop the EEG procedure at any time.

2. On rare occasions (~5% of the time), temporary redness of skin is noted following an EEG in locations where sensors were placed. Redness of skin will generally resolve within a few minutes without discomfort.

3. On rare occasions (~5% of the time), the placement of the sensors on the skin will cause a very small portion of the skin, less than 1 centimeter, to swell slightly; this might appear like a very small welt. This is caused by the retention of moisture under sensors and goes away soon after the sensors are removed.

Other Risks:

View: Risk Detail Entry

Address for each screening procedure, research intervention/interatction, and follow-up/monitoring procedure:

* Research Activity:

Self Report Questionnaires

Common Risks:

There are no common risks associated with this procedure.

Infrequent Risks:

It is possible that participants could experience psychological distress due to questions included on self-report questionnaires. However, participants will be informed that they can skip questions they do not wish to answer.

Other Risks: