Suvorexant for Opioid/Stimulant Co-use

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JHM IRB - eForm A – Protocol

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1. Abstract

The opioid epidemic has led to an unprecedented rise in opioid use disorder (OUD) cases and overdose deaths. In recent years, these increases have been accompanied by a rise in opioid/stimulant co-use, an issue that has existed for decades and for which no effective treatment has ever been identified. Current increases in opioid overdose deaths are now largely driven by stimulant co-use. Thus, innovative treatments that are safe and effective among patients co-using opioids and stimulants are urgently needed. Suvorexant (SUVO) is an FDA-approved medication used to treat insomnia. SUVO interacts with the brains reward system in such a way that it may reduce craving for stimulants in persons using opioids, and we recently also found that SUVO reduced craving and increased total sleep time among individuals who were withdrawing from opioids. That study also showed that SUVO was extremely safe and well-tolerated in persons using opioids.

This between-subjects, double-blinded, randomized controlled pilot study will recruit patients who are receiving methadone or buprenorphine treatment for OUD and are using cocaine. Participants will be randomly assigned to receive 28-30-days of SUVO or placebo. They will visit the clinic regularly to provide urine drug screens and complete questionnaires and will wear a device that can measure their sleep parameters. We expect that relative to persons who receive placebo, individuals who receive SUVO will 1) be less likely to screen positive for cocaine and/or opioids on urine drug screens, 2) will report lower drug craving, 3) will have better sleep continuity (i.e., longer total sleep time, shorter wake after sleep onset, and greater self-reported sleep quality, and 4) will report overall lower stress and better mood than persons who receive placebo. We also expect that patients will not have side effects from SUVO. These preliminary data will inform whether this FDA-approved medication may help patients stop co-using opioids and stimulants, which can be scaled up to reduce public health consequences related to co-use.

2. Objectives (include all primary and secondary objectives)

Primary Aim 1. Examine whether individuals who are randomly assigned to SUVO 20mg (oral) will be less likely to test positive for (i) cocaine and (ii) non-prescribed opioids on urine drug screens (UDS) and will self-report lower opioid and cocaine craving, relative to those receiving placebo.

Secondary Aim 1. Examine whether, relative to placebo, SUVO 20mg will improve self-reported sleep quality and total sleep time, as assessed via a sleep diary and an actigraph-like device, and will reduce self-reported insomnia symptoms and wake after sleep onset (WASO).

Secondary Aim 2. Given previous work suggesting that Suvorexant has a good safety profile among patients using opioids and patients using cocaine, a secondary aim will test no between-group differences in the rate of adverse events between individuals assigned to Suvorexant and placebo.

Secondary Aim 3. Examine whether SUVO 20mg will be associated with lower stress reactivity, lower self-reported stress and negative affect, and greater positive affect, relative to placebo.

3. Background (briefly describe pre-clinical and clinical data, current experience with procedures, drug or device, and any other relevant information to justify the research)

Opioid/stimulant co-use is a public health crisis that is increasing in prevalence (Goodwin et al., 2021) and directly contributing to increases in overdose deaths and disproportionately impacting minority individuals (Townsend et al., 2022). Individuals engaged in opioid/stimulant co-use face a greater risk of treatment discontinuation and continued substance use (Levin et al., 2015).

Chronic opioid exposure can produce supersensitivity in dopamine neurons that could (theoretically) increase the reinforcing effects of cocaine in persons with OUD (Strickland et al., 2022). This testable theory may explain why new onset stimulant use develops in persons who are receiving opioid agonist treatment of OUD, a trend that has been observed for decades but for which no effective treatment has ever been identified. The following proof-of-concept study will examine whether antagonizing the orexin system with suvorexant (SUVO) will reduce cocaine co-use in persons receiving methadone or buprenorphine treatment. SUVO is an FDA-approved medication for treatment of insomnia, that has also shown substantial promise in reducing opioid craving and withdrawal symptoms.

This approach is supported by preclinical evidence that orexin antagonism blocks morphine sensitization of the ventral tegmental area (Mazaheri et al., 2022) and interacts meaningfully with the reward pathway and may have both direct effects on cocaine use and indirect effects by way of reducing opioid sensitization (Aston-Jones et al., 2010). This is also supported by our Phase II study that showed SUVO 20mg produced significant and clinically-meaningful reductions in opioid craving, insomnia, and withdrawal in persons withdrawing from opioids, a good safety profile, no evidence of abuse potential, and no SUVO discontinuation symptoms (Huhn et al., 2022). Further support suggested that SUVO improved restful sleep and reduced wake after sleep onset among patients using cocaine (Suchting et al, 2020). Additionally, SUVO has an excellent safety profile; previous studies examining SUVO in populations who use substances reported no serious adverse events (Huhn et al., in press; Suchting et al., 2020). SUVO also has also been shown to have low abuse liability (Herring et al., 2016; Huhn et al., 2022), and does not produce withdrawal symptoms after discontinuation (Herring et al., 2016).

4. Study Procedures

a. Study design, including the sequence and timing of study procedures (distinguish research procedures from those that are part of routine care).

Study Overview: Participants who are in methadone or buprenorphine treatment for OUD and are using cocaine will be recruited from the community to visit the clinic twice weekly and provide urine tests that will be analyzed for evidence of recent drug use and complete self-reported measures. All participants will be randomized to receive double-blinded doses of suvorexant (20mg, oral, QD) or placebo, which will be dispensed in blister packages for 28-30 days. Medication will be over-encapsulated and will include either 10mg SUVO or placebo. Participants will be expected to take 2 capsules each night and will be informed they can reduce their dose to 1 capsule per night if desired (these data will be documented as a secondary outcome).

Recruitment: Participants will be recruited from the community using social media advertisements, flyers, and newspaper advertisements. Recruitment will also include review of clinical records of individuals who are not clinical patients of the PI or co-investigators prior to their consent at Man Alive. At ATS, recruitment will include referral of individuals specifically for research purposes by treating clinicians not on the study team and recruitment of individuals who are patients of the study co-investigators. Interested individuals will complete a brief screening to determine initial eligibility before completing a full eligibility screen.

Screening visit(s). Screening procedures may be scheduled across more than 1 day to meet participant schedules. Prior to completing any study-related screening, participants will review and sign an informed consent form with a trained staff member. Participants will be given the opportunity to do an in-person or a remote consent. For participants that complete the remote consent, some screening procedures will also be completed remotely, including interviews and questionnaires. Participants who complete this initial eligibility screening will complete the remainder of their screening visit in person. During the screening visit, participants will be assessed for inclusion and exclusion criteria. A urine drug-screen will be collected to assess for recent drug exposure and pregnancy (when indicated), the Mini-International Neuropsychiatric Interview (M.I.N.I.), the Addiction Severity Index (McLellan, Cacciola, & Zanis, 1997), the Columbia Suicide Severity Rating Scale, a demographic questionnaire, and a health form assessing current conditions and medications will be used to help evaluate participant eligibility.

Baseline/Randomization visit. Following determination of eligibility, participants will be randomized (stratified by gender) to receive 20mg of SUVO (the maximum FDA approved dose) or placebo. Randomization will occur prior to visit 1. At the randomization visit, participants will provide a urine sample that will be tested for recent drug use and complete self-report measures as described below. They may also complete a cue-induced craving paradigm, a probabilistic reward task, and the Trier Social Stress Test (TSST) described below. Participants will also be provided with an actigraph-like device to wear for the duration of their study participation to assess sleep.

Medication dispensing will begin during the baseline session. Participants will receive a blister package with 7-days of medication dispensed as two capsules (10mg SUVO or placebo) so that medication doses can be reduced to 50% of the dose if requested by a

participant. Participants will also receive a 3-day blister package as a contingency strategy in case of missed visits. Participants will be instructed to return blister packages once weekly as a measure of medication compliance.

Weekly visits. Participants will complete visits twice weekly during the study period. At these visits, participants will be asked to complete a urine drug screen and self-report measures as described below. Medication will be dispensed once weekly during these visits.

Final/Exit visit. The final study visit will be collected at day 28-30 (+7 days) or the final day of study participation. At their final visit, participants will complete a urine drug screen and self-report measures, and tasks. Participants will be able to request SUVO prescriptions from their provider if desired and all participants can request study drug unblinding after data collection is closed.

Follow-up phone visit: Participants will be contacted via phone after the final/exit visit. Information will be collected on their experience during the study, any changes in symptoms following study exit, treatment plans going forward, and other feedback regarding the study.

Sleep diaries: To facilitate scoring of actigraphy data, participants will be asked to complete nightly sleep diaries.

The following study Measures may be used:

- Mini-International Neuropsychiatric Interview (M.I.N.I.): The MINI is a semi-structured interview that will be used to assess presence of stimulant use disorder.
- Addiction Severity Index: The ASI will be used to collect information related to severity of recent substance use disorder
- Columbia Suicide Severity Rating Scale: The C-SSRS is the standard for assessing present risk for suicidality. It will be administered at screening and end of study, and point prevalence during the study as indicated.
- Demographic questionnaire. This will ask participants basic demographic information (e.g., gender, age, race, ethnicity, employment status, etc.)
- Medical History: A self-reported medical history will be collected to determine eligibility for suvorexant administration.
- Assessment of previous medication administration: Participants will be asked whether they have ever received a number of different medications, either illicitly or through a prescription.
- Medication expectancy questionnaire. Participants will be asked to rate how much they expect to like the study drug, as well as how much they expect the study drug to help improve various symptoms (i.e., opioid use, cocaine use, sleep, stress).
- Medication Satisfaction and Blinding: Medication satisfaction and a question assessing whether participants believe they received the active or inactive medication will be collected at the final study visit.
- Caffiene intake: A self-report measure of caffeine use will be given.
- Fagerstrorm Test for Nicotine Dependence: This is a validated measure of problematic nicotine use.
- Distress intolerance. The Distress Intolerance scale will be used to identify the extent to which individuals have difficulty tolerating aversive states.

- Affect-based impulsivity. The UPPSP impulsive behavior scale is a measure of five subtypes of affect impulsivity: positive urgency, negative urgency, lack of perseverance, lack of premeditation, and sensation seeking.
- Visual Analog Ratings: Participants will be asked to complete visual analogue scales assessing craving substances, at each assessment and, at some timepoints, when presented with visual cues.
- Trier Social Stress Test: Trier Social Stress Test (TSST; Kirschbaum et al., 1993), a 15-minute, well-validated psychosocial stress induction paradigm in which participants are asked to prepare and perform a speech, as well as mental arithmetic, in front of an experimenter.
- Probabilistic Reward: Participants will be asked to complete a validated probabilistic reward task (Pizzagalli et al., 2008), in which they will be asked to discriminate between two similar stimuli, one is associated with a higher degree of reward. This task takes approximately 25 minutes and is a behavioral measure of anhedonia.
- Brief Pain Inventory: Participants will self-report their pain symptoms, and pain interference.
- Insomnia Severity Index: Participants will self-report insomnia symptoms.
- Positive and Negative Affect Schedule: The PANAS will be used to assess changes in affect as a function of study medication. It will be administered at screening, during weekly visits, and end of study.
- Pittsburgh Sleep Quality Index: The PSQI is a validated measure of sleep quality and sleep patterns.
- Perceived Stress Scale: Participants will self-report their perceived stress.
- GAD-7: The GAD-7 is a 7-item self-report measure of anxiety symptoms.
- Sleep Diary: Participants will self-report their previous nights sleep.
- Subjective Opiate Withdrawal Scale: Participants will self-report whether they are experiencing opioid withdrawal symptoms.
- Hypothetical purchase tasks: Participants will complete several questions asking how much they would purchase of various substances at various prices.
- Hypothetical Monetary Choice: Participants will ask whether they would hypothetically prefer a smaller amount of money at a shorter time interval, or a larger amount of money after a delay.
- Blood pressure, heart rate, and weight
- Opioid/cocaine cued choice: A paradigm in which participants will be shown two images (cues: one cocaine or opioid and one control image) presented side-by-side followed by concurrent monetary offers below each image.
- Time since last methadone or buprenorphine dose.
- Time Line Follow Back: Participants will be asked to identify “anchor events” in the time period assessed, and will then be prompted to report on their substance use, using anchor events as a guide.
- Urine Drug Screen: Qualitative tests will be used to assess evidence of recent exposure to illicit substances such as opioids, cocaine, methamphetamine, benzodiazepines, fentanyl, and cannabis. Tests will also confirm presence of buprenorphine or methadone.
- STOP-BANG questionnaire will be used as a screening measure for sleep apnea.

b. If your study involves data/biospecimens from participants enrolled under other research studies with a written consent or under a waiver of consent, please list the IRB application numbers for those studies. Please note: Certificate of Confidentiality (CoC) protections applied to the data in source studies funded by NIH or CDC will extend to this new study if the funding was active in 2016. If this situation applies, Section 36, question 6 in the application will need to be answered "Yes" and "Hopkins Faculty" should be selected in question 7. No other documents are required.

N/A

c. Study duration and number of study visits required of research participants.

Participants will complete 9-10 visits (10 visits if a screening visit is broken into two visits for participant convenience) across a period of approximately 5-6 weeks: a screening visit(s), a baseline/randomization visit and 8 twice weekly visits between the 28-30 days of SUVO administration. The estimated study duration is 1 year.

d. Blinding, including justification for blinding or not blinding the trial, if applicable.

Participants will be blinded to whether they received SUVO vs. placebo. This is meant to enhance study rigor and control for expectancy effects.

e. Justification of why participants will not receive routine care or will have current therapy stopped.

There is no current routine care for stimulant use disorder. Participants will not be removed from routine care and will continue participating in their treatment for OUD as indicated.

f. Justification for inclusion of a placebo or non-treatment group.

Inclusion of a placebo group will be necessary to determine if SUVO is efficacious in improving outcomes for patients receiving treatment for OUD and using cocaine.

g. Definition of treatment failure or participant removal criteria.

Participants will be removed from the study if they opt out or if the medical team determines it is not safe to continue in the study or if they request to discharge from the study. Participants who become pregnant, are incarcerated or hospitalized for $\geq$7 days, end their OUD treatment, or rescind consent/ask to be discharged will be removed from the study. Additional stopping rules will include not abiding by study policies and procedures, or engaging in behaviors towards staff or other participants that are abusive. Finally, development of an intercurrent illness or condition that changes the participant's risk profile may result in a medically-related discharge from the study.

h. Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely.

Participants will continue to receive their clinically-indicated care for OUD treatment. Participants will be able to request a suvorexant prescription from their PCP if interested in continuing with the study medication after study completion.

i. If biological materials are involved, please describe all the experimental procedures and analyses in which they will be used.

Urine drug screens will be used as an outcome in this analysis. Urine drug screens will be taken at each visit using biochemical urine panel dip stick tests. The research coordinator will record the result of the urine drug screen. Urine specimens will be stored for future research.

5. Inclusion/Exclusion Criteria

Inclusion criteria:
1) Ages 18-65,
2) Meet DSM-5 criteria for stimulant use disorder,
3) Currently receiving methadone or buprenorphine treatment for OUD and considered to be stable on current dose for at least 30 days;
4) Willingness to engage with study protocol,
5) Use of birth control (as appropriate),

Exclusion criteria:
1) Psychiatric or medical conditions that are judged by the investigators to interfere with participation or that are contraindicated for use with SUVO,
2) Pregnant or breastfeeding,
3) Current use of benzodiazepines, tranquilizers, or other schedule IV sleep medications,
4) Moderate or severe substance use disorder other than opioid, stimulant, or cannabis use disorder;
5) SUVO consumption in the last 30 days,
6) Use of medications that are contraindicated with the study;
7) Past 30-day suicidal behavior,
8) Use of continuous positive airway pressure (CPAP) device for sleep apnea.

6. Drugs/ Substances/ Devices

a. The rationale for choosing the drug and dose or for choosing the device to be used.

Suvorexant (SUVO) is a dual orexin receptor antagonist (DORA) and an FDA-approved medication for treating insomnia. The 20mg dose is the maximum approved dose for use by the FDA. Our recent study demonstrated that a dose of SUVO 20mg reduced craving, insomnia symptoms, and withdrawal in persons undergoing opioid withdrawal (Huhn et al., 2022). Other research groups have found SUVO can improve restful sleep and reduced wake after sleep onset among individuals using cocaine (Suchting et al., 2020). SUVO has a strong safety profile, low abuse liability, and dose not produce withdrawal symptoms after discontinuation (Huhn et al., 2022; Suchting et al., 2022; Herring et al., 2016). Importantly, SUVO is hypothesized to restore

dopaminergic functioning, which we believe is disrupted in persons who are co-using opioids and stimulants and is the mechanistic reason we are evaluating SUVO in this study.

b. Justification and safety information if FDA approved drugs will be administered for non-FDA approved indications or if doses or routes of administration or participant populations are changed.

We are proposing to administer SUVO 20mg, which is an FDA-approved dose. We are not requiring insomnia as an inclusion criterion in order to focus more specifically on opioid-stimulant co-use behaviors. We have collected substantial evidence that SUVO is safe and does not increase risk of misuse in persons with OUD (see Huhn et al., 2022).

c. Justification and safety information if non-FDA approved drugs without an IND will be administered.

SUVO is an FDA-approved medication. We are not submitting for an IND because the intervention is not intended to be reported to the FDA as a well-controlled study or for a significant label change, it is not intended to support a significant change in the advertising for the product, and it does not involve a route or dose level or patient population for which there is increased risk associated with use of the drug.

7. Study Statistics

a. Primary outcome variable

Urine drug-screen results. Participants will complete a urine drug screen at each clinic visit. The presence or absence of non-prescribed opioids and/or cocaine will be recoded at twice-weekly sessions. The primary outcomes will be 1) the presence of absence or opioids at each screen, 2) the presence or absence of cocaine at each screen, and 3) the presence or absence of a screen that is negative for all illicit substances.

Self-reported opioid and cocaine craving. Participant will complete visual analogue scale measures of opioid and cocaine craving during each weekly visit. The average score across each visual analogue scale with be a primary outcome.

Opioid and cocaine cue reactivity. Participants will also complete visual analogue scales in the presence of drug cues. Average scores on visual analogue scales will serve as a primary outcome

b. Secondary outcome variables.

Insomnia Severity Index Scores. The Insomnia Severity Index is a seven-item screening measure of insomnia. Items are rated on a five-point scale. A cut score of 15 is typically used to demark clinical insomnia. The scale has been shown to have excellent psychometric properties, including among patients with substance use disorders.

Sleep Continuity. Using actigraphy and sleep-diaries (in which persons will be asked to report on their sleep the night before the assessment), we will focus on three commonly used sleep continuity outcomes: 1) total sleep time (TST), or the total number of minutes that an individual

is asleep, 2) wake after sleep onset (WASO), or the total number of minutes that an individual is awake after sleep onset and prior to awakening, and 3) subjective sleep quality.

Co-occurring affective symptoms. Participants will be assessed for positive and negative affect using the PANAS. Participants will report perceived stress using the Perceived Stress Scale (PSS) is a 10-item measure of perceived stress. Items are rated on a five-point scale.

Abuse Liability Assessments (i.e., Medication Satisfaction Questionnaire). Participants will be asked to complete abuse liability measures. Participants will also be assessed for adverse events and serious adverse events in each visits. The abuse liability of the blinded study drug will be assessed by asking participants to rate "drug effects", "good effects", and "bad effects", on a 0-100 point VAS, with 0 being "None" and 100 being "Extremely". Participants will also report the perceived street value of the study drug. These subjective drug effect ratings are considered by the FDA to be the gold standard for assessing abuse liability.

Adverse events We will follow standard FDA guidelines regarding adverse events. Participants will be able to self-report adverse events via a study contact number. Events will be documented on a standardized form that adheres to FDA standards for adverse event reporting (e.g., event, system affected, start and stop date/time, perceived relationship to the study, severity, expectedness).

c. Statistical plan including sample size justification and interim data analysis.

Primary Aim 1. To examine whether SUVO 20mg reduces opioid and cocaine use and craving relative to placebo, a series of mixed models will be conducted. For analyses with a binary outcome (i.e., use at each assessment), generalized logistic models will be used, and for analyses with a continuous outcome (i.e., craving), linear mixed models will be used. Mixed effects models will also be used to compare drug cue reactivity at baseline and during the final week. For each model, we will include main effects of timepoint and medication group, as well as an interaction term. If the two treatment groups are systematically different on demographic or use characteristics at baseline, these measures will be included as covariates in the analysis. Models will involve a random intercept.

Secondary Aim 1 and 3. To examine whether SUVO 20 mg improves 1) insomnia symptoms, 2) indices of sleep continuity, and 3) co-occurring affective symptoms relative to placebo, a series of mixed effects models will be conducted. For each model, we will include main effects of timepoint and medication group, as well as an interaction term. If the two treatment groups are systematically different on demographic or use characteristics at baseline, these measures will be included as covariates in the analysis. Models will involve a random intercept. Mixed effects models will also be used to compare drug cue reactivity at baseline and during the final week.

Secondary Aim 2. To compare SUVO 20mg to placebo on number of adverse events experienced, t-tests will be used.

Power analysis and sample size. A sample size of 40 will be used in this study. For all aims, we are sufficiently powered to detect moderate-to-strong effect, which has been observed in

previous studies (e.g., Huhn et al., 2022). Due to our smaller sample size, effect size measures will also be considered.

All analyses will be conducted in SPSS and R. Two-tailed tests and an alpha level of .05 will be used.

d. Early stopping rules.

Participants will discontinue the study if the medical team determines it is not safe to continue in the study or if they request to discharge from the study. Additional stopping rules will include not abiding by study policies and procedures, or engaging in behaviors towards staff or other participants that are abusive. Finally, development of an intercurrent illness or condition that changes the participant's risk profile may result in a medically-related discharge from the study.

8. Risks

a. Medical risks, listing all procedures, their major and minor risks and expected frequency.

Suvorexant is a Schedule IV dual orexin receptor antagonist (DORA) that is FDA-approved for the treatment of insomnia. Suvorexant is 82% bioavailable and has a Tmax of 2 hours. Tmax can be delayed by food though this does not impact the Cmax. It is extensively metabolized by the liver through CYP3A enzymes. The elimination half-life is 12 hours, and it is excreted through both renal (23% unchanged) and fecal (66%) means. Suvorexant is contraindicated with other CNS depressants and alcohol and strong CYP3A inhibitors. It is rated pregnancy category C, indicating insufficient data available to make determination for human subjects. Suvorexant is contraindicated in patients with narcolepsy, patients with recent suicidal behavior, or patients with severe hepatic impairment. There is no evidence of potential overdose and a toxic dose has not been established. Clinical trials that administered up to 240mg of suvorexant reported no overdose effects, though there was a dose-dependent increase in the frequency and duration of next day somnolence. As per product label, most common side effects are sleepiness/drowsiness (7% of people), headache (7%), dizziness (3%), diarrhea (2%), dry mouth (2%), upper respiratory infection (2%), abnormal dreams (2%), and cough (2%). Serious adverse effects include sleep paralysis (7%), somnolence (7%), and worsening of depression or suicidal ideation.

b. Steps taken to minimize the risks.

Individuals with medical or psychiatric contraindications and/or individuals who are taking exclusionary medications (including CNS depressants such as benzodiazepines or other sleep medications), individuals with co-occurring moderate or severe substance use disorder, those with current and major psychiatric illness (e.g., bipolar disorder) or past 30-day suicidal behaviors are excluded for participating. Participants will be provided the maximum FDA-approved dose (20mg). All medication will be dispensed in two (10mg) capsules and participants will be informed they can refuse reduce from 2 to 1 capsule or stop taking medication at any point and we will track participant acceptance (e.g., in terms of adherence with dosing schedule) of the medication as part of the study. Given that suvorexant can cause next-day drowsiness, participants will be explicitly instructed not to drive or operate heavy machinery under any circumstances within 8 hours of taking suvorexant for the first time, or if they continue to feel

drowsy or have cognitive difficulties after 8 hours post suvorexant dosing. Participants will also be instructed to contact the study team if drowsiness or cognitive difficulties persist for longer than 8 hours after dosing. All participants will be asked to plan alternative transportation strategies if needed.

Participant adverse events (AEs) will be monitored and documented. Participants will be provided with a study contact number in case they experience an adverse event outside of a typical study visit. Events will be documented on a standardized form that adheres to FDA standards for adverse event reporting (e.g., event, system affected, start and stop date/time, perceived relationship to the study, severity, expectedness). We will also document whether concomitant medications were self-administered in response to the event (and the associated medication, dose, route, start and stop date/time, and outcome), whether the event resolved by study discharge, and whether the event met the criteria for a serious adverse event.

All events will be documented by trained staff members and will be disclosed to the study PIs and the study physician daily via daily memos (confidential emails that are sent each night to the study team via secure email system). Events will be discussed by the team at weekly study meetings or more frequently as needed. Any event that exceeds an *a priori* safety threshold, that is unexpected or of unexpected severity, or for which the participant expresses concern, will result in the staff member contacting a medical team member immediately via phone for a consultation. Staff will be instructed to document all adverse reports.

c. Plan for reporting unanticipated problems or study deviations.

All SAEs will be reported to the JHM IRB within 3 working days after a study PI learns of the event. In addition, the study PI will notify the study co-investigators. The PI will coordinate dissemination of subsequent information obtained relating to the death (e.g., autopsy report, hospital records, toxicological analyses).

The Johns Hopkins IRB will be provided with an annual summary of AEs and SAEs as part of the continuing review**.** If any SAEs requires a change to the protocol or consent form, the PI will make those changes promptly and submit the revised documents to the JHM IRB and appropriate other agencies.

Important adverse events that are unanticipated, including pregnancy, will be reported to the Johns Hopkins IRB within 10 working days. If the important adverse events requires changes to the protocol or consent form, the PI will make those changes promptly and submit the revised documents to the IRB and appropriate other agencies.

d. Legal risks such as the risks that would be associated with breach of confidentiality.

We will minimize risk of breach of confidentiality by de-identifying data stored in the master data set. Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Consistent with these regulations a signed authorization will be obtained that informs each subject of the following:

- What protected health information (PHI) will be collected from subjects in this study

- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

e. Financial risks to the participants.

Participants are unlikely to incur financial risks.

9. Benefits

a. Description of the probable benefits for the participant and for society.

The present study will help inform treatment opioid/stimulant co-use, a growing problem in our society.

10. Payment and Remuneration

a. Detail compensation for participants including possible total compensation, proposed bonus, and any proposed reductions or penalties for not completing the protocol.

Compensation: Participants will earn $35 for screening and $40-75 for additional visits (payment varies based on study tasks required), and $10 for completing the phone exit visit, for a total maximum earning potential of $445.

11. Costs

a. Detail costs of study procedure(s) or drug (s) or substance(s) to participants and identify who will pay for them.

Participants will not be required to pay for study drug, or any aspect of study participation.

12. Transfer of Materials

Transfer of biospecimens from Johns Hopkins to another organization for research purposes and receipt of biospecimens from an outside organization for your research must adhere to JHU policies for material transfer (https://ventures.jhu.edu/faculty-inventors/forms-policies/) and biospecimen transfer (https://hpo.johnshopkins.edu/enterprise/policies/176/39187/policy_39187.pdf?_=0.622324232879).

Samples will not be transferred outside of JHU.

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