Document Coversheet

Study Title: A Novel Drug Combination as a Pharmacotherapeutic for Methamphetamine-Use Disorder

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FL Initial Review

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Resubmission	

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FROM: Chairperson/Vice Chairperson
Medical Institutional Review Board (IRB)

SUBJECT: Approval of Protocol

DATE: 7/8/2019

The Medical Institutional Review Board approved minor revisions requested at the convened meeting on 6/13/2019 for your protocol entitled:

A Novel Drug Combination as a Pharmacotherapeutic for Methamphetamine-Use Disorder

Approval is effective from 6/13/2019 until 6/12/2020 and extends to any consent/assent form, cover letter, and/or phone script. If applicable, the IRB approved consent/assent document(s) to be used when enrolling subjects can be found in the "All Attachments" menu item of your E-IRB application. [Note, subjects can only be enrolled using consent/assent forms which have a valid "IRB Approval" stamp unless special waiver has been obtained from the IRB.] Prior to the end of this period, you will be sent a Continuation Review (CR)/Administrative Annual Review (AAR) request which must be completed and submitted to the Office of Research Integrity so that the protocol can be reviewed and approved for the next period.

In implementing the research activities, you are responsible for complying with IRB decisions, conditions and requirements. The research procedures should be implemented as approved in the IRB protocol. It is the principal investigator's responsibility to ensure any changes planned for the research are submitted for review and approval by the IRB prior to implementation. Protocol changes made without prior IRB approval to eliminate apparent hazards to the subject(s) should be reported in writing immediately to the IRB. Furthermore, discontinuing a study or completion of a study is considered a change in the protocol's status and therefore the IRB should be promptly notified in writing.

For information describing investigator responsibilities after obtaining IRB approval, download and read the document "PI Guidance to Responsibilities, Qualifications, Records and Documentation of Human Subjects Research" available in the online Office of Research Integrity's IRB Survival Handbook. Additional information regarding IRB review, federal regulations, and institutional policies may be found through ORI's web site. If you have questions, need additional information, or would like a paper copy of the above mentioned document, contact the Office of Research Integrity at 859-257-9428.

1. BACKGROUND

Methamphetamine (MA) use disorder (MUD) is a significant public-health concern, the magnitude of which is increasing. The number of overdose deaths involving MA increased 2.7-fold between 2010 and 2014 (Warner et al., 2016). In 2015, 225,000-individuals initiated MA use, while 872,000 had MUD, which accounted for over 8% of treatment admissions in the USA (Bose et al., 2016; Substance Abuse and Mental Health Services Administration, 2016, 2017). Between 2010 – 2014, the number of past month MA users increased over 60%. Alarmingly, between 2014 and 2015, MA seizures by law-enforcement agencies increased by 50% (National Drug Control Strategy, 2016). While the number of past month MA users in 2015 (i.e., 897,000) cannot be compared to previous years because of methodological changes in the survey, the concomitant increase in drug seizures by law-enforcement agencies and the number of MA users observed in the past suggests the magnitude of this drug problem will increase in the future (Bose et al., 2016; National Drug Control Strategy, 2016).

Abused stimulants, such as MA, produce their behavioral and physiological effects *via* interaction with monoamine transporters (i.e., dopamine [DA], serotonin [5HT], and norepinephrine [NE]) (Fleckenstein et al., 2000; 2007; Rothman and Glowa, 1995). Moreover, MUD is characterized by perturbations of the DA, 5HT and NE systems (e.g., Kish et al., 2009; Krasnova et al., 2010; Sekine et al., 2003). Stimulants can be broadly categorized into two groups by their mechanism of action at these monoamine transporters: inhibitors (e.g., cocaine) or transporter substrates (e.g., MA). MA elevates extracellular monoamine levels by reversing the process of transporter-mediated exchange, thereby potentiating monoamine efflux. Consistent with these biochemical data, interaction with each of these monoamine systems independently contribute to the abuse-related effects of MA (Howell and Kimmel, 2008; Howell and Negus, 2014; Kirby et al., 2011; Sofuoglu and Sewel, 2009). Moreover, MUD is characterized by perturbations of the DA, 5HT and NE systems (e.g., Kish et al., 2009; Krasnova et al., 2010; Sekine et al., 2003). These findings suggest that therapeutics for monoamine systems are a logical target for developing medications for MUD.

DA systems have been targeted extensively because they play a prominent role in the abuse-related effects of MA as well as MUD. Methylphenidate (MTH), a high affinity DA transporter inhibitor widely used to manage Attention-Deficit/Hyperactivity Disorder (ADHD). In the seminal trial (Tiihonen et al., 2007), the efficacy of 54 mg/day methylphenidate (MTH) or placebo was determined in amphetamine-dependent patients. Among those who completed the trial, MTH-treated patients had significantly fewer amphetamine-positive urines relative to their placebo-treated counterparts. In a more recent trial (Rezaei et al., 2015), the efficacy of MTH (up to 54 mg/day) or placebo was determined in MA-dependent patients. MTH was safe and tolerable, and MTH-treated patients had significantly fewer MA-positive urine samples than placebo-treated patients during the tenth week of the trial. In another trial, the efficacy of MTH (54 mg/day) or placebo in combination with motivational incentives for MA-negative urine drug screens and cognitive-behavioral therapy was determined in MA-dependent patients (Ling et al., 2014). MTH reduced MA use days during weeks 1-10 and 14 relative to the placebo group. The groups did not differ in terms of MA-positive urine tests during the last 30 days of the active phase of the trial. In two trials, placebo- and MTH-treated patients did not differ in terms of MA-positive urine tests or craving (Konstenius et al., 2010; Miles et al., 2013). d-Amphetamine, an indirect DA agonist used for ADHD, was ineffective in two trials, although it significantly attenuated MA withdrawal symptoms and MA craving relative to placebo (Galloway et al., 2011; Longo et al., 2010). Overall, MTH was effective in some, but not all, clinical trials. While these data suggest continued research with MTH for MUD is warranted, novel strategies are needed to enhance its efficacy. One approach would be to combine MTH with another medication that targets other monoamine systems.

Within the scope of 5HT and NE systems, the results of an elegant randomized, placebo-controlled, human clinical pharmacology study are germane to the present study (Hysek et al., 2012). This study used a 2 X 2, double-blind, placebo-controlled, randomized, crossover design to determine whether duloxetine (DUL), an antidepressant with high affinity for 5HT and NE transporters, attenuates the subjective and biological effects of 3,4–methylenedioxy-methamphetamine (MDMA). Subjective and physiological effects were assessed before MDMA or placebo administration and hourly for five hours.

MDMA alone produced robust increases in prototypical subjective and cardiovascular effects of stimulants. DUL significantly attenuated the subjective effects and cardiovascular effects of MDMA. Pharmacokinetic (PK) analysis indicated that these effects were not due to DUL altering MDMA levels. These results suggest DUL might be effective for amphetamine-use disorders.

We propose to demonstrate the initial efficacy of an innovative pharmacological strategy for MUD: Triple Monoamine-Uptake Inhibition. Triple monoamine uptake inhibitors are under development for depression and obesity, but are yet available for use with humans (Popik et al., 2006; Tran et al., 2012; Skolnick, 2012; Skolnick and Basile, 2007; Tizzano et al., 2008; Yang et al., 2012). Triple monoamine-uptake inhibition can, however, be achieved by combining available medications. Given that MTH has high affinity for the DA transporter, but lower affinity for the 5HT and NE transporter, and that DUL has high affinity for the 5HT and NE transporters, but lower affinity for the DA transporter (Bymaster et al., 2001). In this study, we will combine DUL and MTH to functionally produce a triple monoamine-uptake inhibitor with high affinity for the DA, 5HT and NE transporters. We are unaware of any human clinical pharmacology research evaluating triple monoamine uptake inhibition as pharmacologic strategy for MUD. We hypothesize that triple monoamine inhibition via maintenance on DUL-MTH reduces MA self-administration under controlled laboratory. This study will: 1) demonstrate that DUL-MTH combinations attenuate MA self-administration; 2) identify the most efficacious DUL-MTH dose combination that attenuates MA self-administration, and 3) show that DUL-MTH is safe and well tolerated when combined with MA.

2. OBJECTIVES

The primary objective of this study is to demonstrate that MTH-DUL maintenance reduces MA self-administration to a greater degree than placebo, MTH or DUL alone. We will also include a battery of subject-rated and physiological measures to more fully characterize the influence of MTH-DUL maintenance on the effects of MA.

3. STUDY DESIGN

This study will use a double-blind, placebo-controlled design with subjects randomly assigned to DUL dose conditions (i.e., DUL dose is a between-subject factor) and all subjects receiving all MTH doses (i.e., MTH dose is a within subject factor).

4. STUDY POPULATION

Up to 200 individuals will be screened to participate in this study. We intend to enroll 28 (14 male and 14 female) completers into the study. These individuals must be English-speaking, English-reading subjects 18-55 years of age of varying ethnic backgrounds and they will be recruited to participate as inpatients for approximately one month. Enrollment in this study will occur between July 1, 2019 and June 30, 2021. Participants will be required to provide legal proof of age. Subjects must be healthy and without contraindications/allergies to MA, MTH, or DUL. Participants must also report recent use of MA verified by a MA-positive urine. Participants must meet diagnostic criteria for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) for MUD using the Structured Clinical Interview for the DSM (SCID). Screening procedures for all participants will include a medical history questionnaire, laboratory chemistries (blood chemistry screen, complete blood count, ECG and urinalysis) and a brief psychiatric examination. These procedures will be conducted under our lab's screening protocol (Institutional Review Board [IRB]#: 44379). Chemistry values and screening outcomes must be deemed normal. If chemistry values or screening outcomes fall outside normal ranges, the study physician must deem them clinically insignificant for a subject to be enrolled. An electrocardiogram must also be within normal limits, or deemed by a cardiologist to not have any contraindication to study participation. Participants must have a body mass index (BMI) between 19 and 35 to be enrolled. Any potential participant with a history of serious physical disease, current physical disease, impaired cardiovascular functioning, chronic obstructive pulmonary disease, history of seizure or current or past histories of serious psychiatric disorder that in the opinion of the study physician would interfere with study participation will be excluded from participation. Participants with current or past histories of substance

use disorders that are deemed by the doctor to interfere with study completion will also be excluded from participation. Female and male participants must be using an effective form of birth control (e.g., birth control pills, surgical sterilization, IUD, cervical cap with a spermicide, condoms or abstinence) in order to participate. A urine pregnancy test will be conducted before the start of each experimental session to ensure that female participants do not continue in the study if pregnant. All study participants will be judged by a study physician, Dr. Lon R. Hays or Dr. Abner O. Rayapati, to be healthy.

Inclusion Criteria:

1) English-speakers, informed about possible identity verification (driver's license or a passport).
2) Non-treatment seeking male and female subjects between 18 and 55 years of age.
3) Recent use of inhaled, smoked or injected MA verified by a MA positive urine
4) Fulfill DSM-5 diagnostic criteria for MUD reviewed by a psychiatrist
5) Physically healthy, as determined by medical-history questionnaire, drug-use questionnaire, physical examination, laboratory chemistries (i.e., blood chemistry screen, complete blood count, urinalysis and serum pregnancy test for females), electrocardiogram (ECG; as read by a cardiologist and must also be within normal limits, or deemed by a cardiologist to not have any contraindication to study participation) and a mini-mental status examination.
6) A total body weight of >50 kg (110 pounds) and a body mass index (BMI) from > 18 to less than or equal to 35 at screening.
7) Females must be using an effective form of birth control:
   i. Cannot be pregnant.
   ii. Cannot be lactating.
   iii. Must be unable to conceive (i.e., surgically sterilized, sterile, or post-menopausal defined as 1 year without bleeding or spotting) OR must agree to use an acceptable method of birth control (e.g., birth control pills, intrauterine device [IUD], or a double barrier method of birth control (condoms and spermicide together; or diaphragm, condom and spermicide together).
8) No contraindications/allergies to MA, DUL or MTH
9) Not physically dependent on opioids (i.e., provide an opioid negative urine in the absence of opioid withdrawal signs).
10) Subjects must be able to provide and be competent to sign an informed consent form for participation in the study.
11) Male subjects must be using an effective form of birth control (e.g., condoms with spermicidal lubricant, surgical sterilization, abstinence).

Exclusion Criteria:

1) Has DSM-5 diagnosis of current substance use disorder for any psychoactive substance other than nicotine, caffeine, or methamphetamine.
2) Seeking treatment for a substance-use disorder.
3) Has current alcohol use disorder that is judged to require medically supervised detoxification.
4) Undergoing separate drug testing as a condition of probation or as mandated by a government agency (e.g., social services) or a court.
5) Homelessness
6) Is currently participating in or screening for potential participation in another clinical trial of an investigational (un-marketed) medication or has participated in any clinical trial of an investigational medication within 6 months prior to providing informed consent.
7) Has, in the opinion of the study physician, any of the following:
   i. Clinically significant hepatic, renal, or gastrointestinal disorders that could alter absorption, metabolism, or excretion of study drugs.
   ii. Uncontrolled hypertension, significant heart disease (including report or documentation of myocardial infarction within one year prior to randomization), valvular heart disease, or symptomatic orthostatic hypotension.

iii. Any clinically significant ECG abnormality at screening, as determined by the study physician.
iv. History of cerebrovascular disease or stroke. Persistent hypertension (≥ 150/100 mmHg) during screening (i.e., at four consecutive visits during the screening process).
v. Diagnosis of severe chronic obstructive pulmonary (COPD) and/or pulmonary hypertension.
vi. Uncontrolled and/or unstable metabolic and/or endocrine disorder.
vii. History of seizure (excluding childhood febrile seizure), history of head trauma with loss of consciousness for more than 5 minutes, cancer diagnosis in the last 5 years, or any other medical or neurological disorder that would place the subject at greater risk or prejudice evaluation of the safety and efficacy of the study drug.
viii. Any clinically significant laboratory values outside of the normal range as determined by the study physician.
ix. Lifetime history of a major psychiatric disorder (e.g., meets the DSM-5 criteria for schizophrenia, bipolar I and II disorder, or any other psychotic disorder). NOTE: Participants with lifetime history of major depressive disorder, generalized anxiety disorder, dysthymia, social phobia, or specific phobia may be enrolled in the study if they are not on medications.
x. Subjects with a history of suicide attempt or any suicidal behavior in the past 2 years, as assessed using the Columbia-Suicide Severity Rating Scale (C-SSRS). History of suicidal ideation with intent/plan in the past 6 months (a "yes" to Questions 4 and/or 5 on the C-SSRS)

8) Positive family history of cardiovascular disease (e.g., sudden death, ventricular arrhythmia), psychotic disorder, schizophrenia or seizure disorders (except h/o childhood febrile seizure) in a first-degree relative where in the opinions of the study physicians, Drs. Hays, Rayapati, or Gurley, that could increase risk to the participant.
9) Pregnant or nursing (females only).

During the initial screening process, potential subjects will be asked to provide a urine specimen that will be screened for the presence of amphetamine, benzodiazepines, barbiturates, cocaine, MA, tetrahydrocannabinol (THC), and opioids. In order to participate in an experimental session, subjects must provide a urine negative for barbiturates, benzodiazepines, and opioids on each day of their participation. Participants will be allowed to continue if they test positive for MA, if it is determined that this drug was given in a recent session and it is likely that the result is positive due to experimental administration. Dr. Hays or Dr. Rayapati will be notified of MA-positive urines on experimental session days and sessions will only proceed if participants pass the sobriety test and have vital signs within acceptable limits (see below). Participants will be maintained on a caffeine-free diet and will have to abstain from alcohol for the duration of their participation.

5. SUBJECT RECRUITMENT METHODS AND PRIVACY

Subjects are recruited primarily through formal advertisement (i.e., regular newspaper advertisements placed generally in free newspapers), local flyers posted in public areas (e.g., bars, restaurants, stores) and by word-of-mouth. These advertisements are approved under our screening protocol (IRB # 44379). Participants make initial contact by phone with one of our recruiters who have completed the research training and HIPAA compliance web-based modules. If the subject self-discloses information that would make him/her potentially eligible for the study, they will be invited to a screening appointment. Screening is completed by one of our research assistants at the UK Laboratory of Human Behavioral Pharmacology (LHBP). Study investigators may interact with subjects in this setting and appropriate cautions are in place to ensure privacy during the intake process.

6. INFORMED CONSENT PROCESS

All potential subjects that are identified using the subject recruitment methods noted above will provide informed consent prior to participating in the protocol. Subjects that meet the eligibility criteria noted above will come to the LHBP and will undergo a field sobriety test and provide an expired air sample

that will be tested for the presence of alcohol. If the subject passes the field sobriety test (walk and turn, one-leg balance [timed], finger-to-nose and backwards-counting tasks) and the expired air sample is negative, he or she will then be given a copy of the approved informed consent document to read and sign. After reading the consent document, the PI or one of the Co-Is on this protocol will address any questions the subject may have in order to assess the subject's understanding of the protocol. After this, the subject will receive a copy of the informed consent document and will sign a form indicating that they have received a copy of the form they read and signed.

7. RESEARCH PROCEDURES

General Procedures. Subjects that meet the inclusion criteria will participate as inpatients at the University of Kentucky Center for Clinical and Translation Sciences – Inpatient Research Unit (CCTS-IRU). Participants will be discharged upon completion of the entire protocol. This experiment will consist of 1 practice session, 1 medical safety session and 12 experimental sessions conducted according to the timeline in Table 1 (see below). After admission, subjects will be allowed to acclimate to the CCTS-IRU for two days before beginning the study. During this time, subjects will be maintained on a caffeine-free diet, receive instructions concerning the details of the daily research procedures and general rules of the inpatient research unit and complete a drug-free "practice" session to familiarize them with the experimental routine and tasks. Participants will then complete a medical safety session to ensure that they tolerate a dose that approximates the maximum daily MA dose available during experimental sessions (i.e., 40 mg). During this session, intranasal MA doses (i.e., 0, 5, 10, and 20 mg) will be administered in ascending order. Administration of MA doses will be separated by 90 minutes. Participants will be excluded from continuing if he/she exhibits hypersensitivity to the effects of MA as described below. The medical safety session will allow us to ascertain whether the DUL cohorts differ in terms of baseline physiological and behavioral responses to intranasal MA.

Participants will be maintained on a caffeine-free diet throughout the duration of their participation, but will be allowed to smoke tobacco cigarettes *ad lib*, except during experimental sessions. In previous studies, we required participants to abstain from using tobacco products during the conduct of the experimental sessions that were 4-8 hours long, which was acceptable. During their participation in the protocol, participants will not be allowed to use e-cigarettes during the study. All participants will provide urine and expired-breath samples daily during study participation. The presence of non-nicotine drugs of abuse not administered experimentally in the research protocol or alcohol will result in immediate dismissal from the study.

Table 1.

Day	Experimental Procedures
1	Admission and acclimation to the CCTS-IRU
2	Acclimation to CCTS-IRU and Practice Session
3	Medical Safety Session. Intranasal MA challenge (i.e., 0, 5, 10, and 20 mg administered in ascending order). Placebo (i.e., 0 mg) administered at 0900. Subjective-effect measures completed 30 min before placebo administration (i.e., 0830), immediately following and at 15-min intervals for 75 minutes. Subsequent MA administrations will be separated by 90 min.
4-7	DUL (0 or 60 mg/day) and MTH (0 mg/day) administered once daily (at 0700) for 4 days.
8-10	Experimental Sessions. MA (0, 10, 20 mg) self-administration. DUL-MTH maintenance continues.
11-14	DUL (0 or 60 mg/day) and MTH (20 mg/day) administered once daily (at 0700) for 4 days.
15-17	Experimental Sessions. MA (0, 10, 20 mg) self-administration. DUL-MTH maintenance continues
18-21	DUL (0 or 60 mg/day) and MTH (40 mg/day) administered once daily (at 0700) for 4 days.
22-24	Experimental Sessions. MA (0, 10, 20 mg) self-administration). DUL-MTH maintenance continues.
25-28	DUL (0 or 60 mg/day) and MTH (60 mg/day) administered once daily (at 0700) for 4 days.
29-31	Experimental Sessions. MA (0, 10, 20 mg) self-administration. DUL-MTH maintenance continues.
32	Discharge

This experiment will require each volunteer to participate for approximately 4.5 weeks. Experimental sessions will be conducted as outlined in the table above. We would like to note four important issues relating to the table above: 1) To avoid experimental testing on weekends, subjects may be maintained on MTH, DUL, their combination or placebo for longer than outlined below (i.e., maintenance conditions may last for two days longer than in the example below). 2) Subjects will be urn randomized to one of the two DUL dose conditions based on sex and MUD severity (mild, moderate, severity). 3) The order of DUL maintenance conditions will be random. 4) If participants leave the protocol for a reason unrelated to study procedures (e.g., a family emergency or dental problems), they may be re-admitted with physician approval to complete the remainder of the protocol, picking up in the condition where they left off (i.e., sessions/dose conditions that have already been completed will not be repeated). Thus, they may not complete the protocol over one approximately 32-day admission, but can complete the protocol over two admissions totaling approximately 32 days.

During their participation in the research protocol, participants will not be allowed to leave the CCTS-IRU, nor will visitors be allowed. Research participants will be allowed to make local telephone calls. Each day after the practice session, subjects will be awakened at 0700 hours and will receive maintenance medication. Daily activities for maintenance days (non-experimental) are outlined Table 2. Medications will not be administered if a subject's heart rate is ≥100 bpm, systolic pressure is ≥150 mmHg or diastolic pressure is ≥100 mmHg. In addition, the UKU side effects scale will be completed daily to monitor for the emergence of side effects. All subjects will provide urine and expired air samples before and daily during study participation. The presence of non-nicotine drugs of abuse or methamphetamine not administered experimentally in the research protocol will result in immediate termination from the research study.

Table 2.

Time	Daily Activities for Maintenance Days
0700	Patient awakened. Vital signs recorded. Medication administered if vitals are within range. Subject eats breakfast.
1200	Lunch is served.
1700	Dinner is served.
1900	UKU administered. Vital signs recorded.
2300	Lights out.

On MA administration days, participants will be awakened at 0700 hours, receive the assigned DUL-MTH dose and eat a standard, fat-free breakfast (cereal with skim milk, 2 pieces of toast with jam or jelly and 8 ounces of fruit juice). Participants that report smoking tobacco cigarettes will then be allowed to have a cigarette and will not be allowed to smoke again until after completing the session. Sessions will begin at 0800 hours. Worth noting is that triple monoamine-uptake inhibitors also reduce impulsivity and anhedonia, both of which are prominent features of stimulant-use disorders including MUD (Franken et al., 2007; Garfield et al., 2014; Hoffman et al., 2006, 2008; Kalechstein et al., 2002; Leventhal et al., 2008, 2010; Moallem et al., 2018; Newton et al., 2004; O'Tousa et al., 2015; Warnock et al., 2012). While not central to the primary hypothesis of the study, improved impulsivity and decreased anhedonia may engender clinically-relevant data for therapeutics development for MUD. To explore whether triple monoamine uptake inhibition improves impulsivity and decreases anhedonia, we have included a battery of tasks that measure inhibitory control (i.e., Attentional Bias-Behavioral Activation task), impulsivity (i.e., Hypothetical Delay Discounting), and andenonia (i.e., Snaith-Hamilton Pleasure Scale). These measures will be completed the morning (i.e., 0815 h) of Day 2 (practice), 8, 15, 22 and 29 (i.e., immediately prior to conduct of the first experimental session of each maintenance phase). Sampling will begin at 0930 hours and will last approximately 1.25 hours. Participants will

remain in a semi-reclined position in a hospital bed for the duration of the experimental session. Self-administration phase (i.e., the progressive ratio) will begin at 1345 hours. At this time, volunteers will complete the pre-drug measures, including the progressive-ratio procedure. Intranasal drug administration will occur at 1430 hours. Physiological and subjective effect measures will be completed 0, 15, 30, 45, and 60 minutes after drug administration. Experimental measures will be completed as outlined in Table 3 below. Behavioral testing will be conducted at the CCTS-IRU. Subjects will be tested using individual laptop computers that automate the different behavioral tasks. After completing each session, no other experimental activities will be scheduled. Participants will be free to engage in recreational activities during non-session times. Participants will be required to be in bed with lights out by 2300h.

Table 3.

Time	Daily Activities for Experimental Days
0700	Patient awakened. Vital signs recorded. Medication administered if vitals are within range. Subject eats breakfast.
0815	If Practice and Sessions 8, 15, 22, and 29, participant completes ABBA, Hypothetical Delay Discounting, and SHAPS.
0900	Vital signs recorded. Computerized tasks completed. ECG monitoring begins.
0930	Vital signs recorded. 0, 10 or 20 mg intranasal MA administered if vitals are within range. Measures completed 0, 15, 30, 45, 60, and 75 minutes after drug administration
1045	Sampling phase ends.
1200	Lunch is served.
1330	Drug Purchase Task completed.
1345	Vital signs recorded. Computerized tasks completed (including progressive-ratio task). ECG monitoring begins.
1430	Vital signs recorded. Portion of intranasal dose earned is administered if vitals are within range. Measures completed 0, 15, 30, 45, and 60 minutes after drug administration
1530	Session ends. Remainder of daily activities identical to those listed in Table 2.

Subjects will be excluded from further research participation if at any time during the experimental sessions MA increases heart rate above 130 bpm, systolic pressure above 180 mmHg, diastolic pressure above 120 mmHg or if clinically significant and/or prolonged ECG abnormalities are noted. Subjects will remain seated for the duration of the experimental session. Between the sampling and self-administration session, subjects will be allowed to eat a standard hospital lunch but will not be allowed to smoke. No experimental activities will be scheduled for the remainder of the day after a self-administration phase. Subjects will be free to engage in recreational activities (e.g., watch television, read, listen to music, arts and crafts, play video or board games). Research subjects will be required to be in bed with the lights out by 2300 hours.

All participants, whether or not they complete the protocol, will be scheduled for follow-up visits 1-and 2-weeks following discharge. Participants will be paid $50 for each follow-up visit. DUL will be tapered (Bitter et al., 2011). Participants who were in the 60 mg/day group will be maintained on 30 mg/day for one week and then 0 mg/day during the second week following discharge. Participants in the 0 mg/day DUL cohort will be maintained on placebo during the discontinuation phase. All participants (both females and males) will be advised to continue using effective birth control methods given the half-life of DUL and the tapering doses during post-discharge. During these follow-up visits at 1-week and 2-weeks post-discharge, suicidal risks will be assessed via the C-SSRS and emergence of adverse events will also be monitored for all subjects.

Medication and MA Administration:

All drugs will be administered under double-blind conditions and under medical supervision. Placebo capsules and placebo powder will contain only lactose. Both will be visually identical to the powder and capsules that contain active drug. MA will be administered under double-blind conditions and under medical supervision. Medications and/or MA will not be administered if heart rate is ≥100 bpm, systolic pressure is ≥150 mmHg, or diastolic pressure is ≥100 mmHg. A volunteer will be excluded from further participation if they exhibit hypersensitivity (i.e., heart rate > 130 bpm, systolic pressure > 180 mmHg, diastolic pressure > 120 mmHg, or clinically significant changes in ECG or body temperature) to the effects of MA alone, the DUL-MTH combinations alone, or MA during maintenance on the DUL-MTH combinations.

Medication Maintenance: Maintenance medications will be administered once daily using delayed-release DUL or long-acting MTH formulations. DUL produces peak blood levels approximately 6 h after dosing, but DUL levels in plasma remain relatively stable for at least 24 h after dosing (Lantz et al., 2003). Participants randomized to 60 mg/day DUL will initially receive 30 mg/day for two (2) days prior to reaching the target dose (i.e., 60 mg/day) prior to completing the MA self-administration sessions. This dosing regimen will allow participants to acclimate to a lower DUL dose before receiving the target dose. The long-acting formulation of MTH produces a biphasic profile peaking 2 and 6 h after dosing (Markowitz et al., 2003). Levels of MTH decrease after the 6 h peak, but are detectable for at least 24 hours. This stable decrease for MTH, especially if given in the morning, will reduce sleep disruptions associated with long-acting MTH administration while also ensuring clinically effective blood levels during participant waking hours. The MTH doses will be tested in ascending order because clinical guidelines recommend increases of 20 mg at weekly intervals to a maximum dose of 60 mg/day. The duration of maintenance needed to reach steady-state plasma concentrations was calculated based on the pharmacokinetic profiles of delayed-release DUL and long-acting MTH, both of which follow first order kinetics. According to first-order kinetics, 4-7 half-lives is needed to attain steady state. The half-life of delayed-release DUL and long-acting MTH is approximately 12 and 5 hours, respectively (Adjei et al., 2014; Sharma et al., 2000). The maintenance period (i.e., at least 4 days) on each dose of DUL and MTH is sufficient to achieve steady state prior to assessing MA self-administration. The use of the proposed formulations of DUL and MTH will result in more stable concentrations of clinically effective doses.

MA Administration: Doses of MA will be prepared individually for each subject by weighing out the appropriate amount of powdered drug (National Institute on Drug Abuse [NIDA] Drug Supply, Rockville, MD) and mixing it with lactose monohydrate powder, N.F. for a total of 50 mg powder. These MA doses are behaviorally active, well tolerated under controlled conditions, and maintain near-maximal levels of self-administration (Lile et al., 2011; Rush et al., 2011a, 2011b, 2018a, 2018d; Stoops et al., 2015).

Primary Outcome Measure:

Modified Progressive-Ratio Procedures. MA self-administration will be assessed under each DUL-MTH condition. The outcome measure for this procedure is number of doses earned. Testing of each dose of intranasal MA involves two phases: 1) Sampling and 2) Self-Administration. *Sampling Phase*: Participants will sample each of the active intranasal MA doses (0, 10, 20 mg) to acquaint them with the drug effects. Participants will receive a single administration of intranasal MA (0, 10, 20 mg) during each sampling session. Before each of these sessions, participants will be instructed to attend to the effects of the intranasal drug because later that day they will be able to work to receive additional doses of the insufflated drug. Participants will complete the subjective-effects questionnaires 30 minutes before the sampling dose of intranasal MA, immediately following and at 15-min intervals for 75 minutes. *Self-Administration Phase*: 5 h after sampling the available MA dose, participants will complete the Self-Administration Phase. Participants will be given 10 opportunities to earn 1/10th of the sampled dose of MA. Participants will be able to earn drug doses by responding on a computer mouse according to a PR schedule. The initial ratio will be 400 clicks. The response requirement for each

subsequent dose will increase by 100 (i.e., 500, 600, 700, 800, 900, 1000, 1100, 1200, 1300). We have conducted several human drug self-administration studies to refine and enhance our ability to determine the initial efficacy of putative pharmacotherapies for stimulant-use disorders (Sevak et al., 2010; Stoops et al., 2010, 2012). The primary hypotheses are: 1) MA will be self-administered; 2) maintenance on DUL or MTH alone will modestly attenuate MA self-administration; and 3) maintenance on the DUL-MTH combinations will robustly attenuate MA self-administration.

Secondary Outcome Measures:

Subjective-Effects Questionnaire: The Drug-Effect Questionnaire will measure various mood and drug effects. This questionnaire has been used extensively in human clinical pharmacology research.

Physiological Measures: Heart rate, blood pressure, and body temperature will be recorded before intranasal MA administration and at 15-minute intervals following each dose throughout the session using a digital monitor (Dinamap Pro 1000 Vital Signs monitor, Critikon Company L.L.C., Tampa, FL). Cardiac rhythmicity (i.e., electrocardiograms [ECG]) will be recorded for 30 minutes before intranasal MA administration and continuously during each experimental session.

Tertiary Outcome Measures:

Attentional Bias-Behavioral Activation: This task is a modified cued go/no-go reaction time task (E-Prime) (Pike et al. 2013, 2017; Weafer and Fillmore 2012, 2015). In this task, 80% of go targets are preceded by a drug image (i.e., MA and/or use paraphernalia) and 20% of go targets are preceded by a neutral image matched on color and shape. For no-go targets, 80% are preceded by a neutral image and 20% are preceded by a MA image. Participants are instructed to respond on the keyboard when a go target is presented and withhold their response when a no-go target is presented. Dependent measures are the proportion of inhibitory failures to no-go targets following go cues (i.e., MA images).

Hypothetical Delay Discounting: Participants choose between $10 available after a specified delay (i.e., 1, 2, 30, 180 or 365 days) and a smaller amount available immediately (e.g., Would you rather have $10 in 30 days or $2 now?) (Richards et al., 1999). An adjusting amount procedure is used to derive indifference values between the delayed standard and immediate adjusting options for each of the five delays assessed. An indifference value reflects the smallest amount of money an individual chooses to receive immediately instead of the delayed standard amount ($10) at the specified delay. Smaller indifference values indicate greater discounting by delay and impulsivity. Higher rates of delay discounting (i.e., smaller indifference values) indicate that a person is not controlled by temporally distal events. Hypothetical choices as measured on similar tasks correlate well with choices that are reinforced (Johnson and Bickel, 2002). Indifference points and area-under-the-curve (AUC) will be calculated (Myerson et al., 2001).

Snaith-Hamilton Pleasure Scale (SHAPS): This 14-item scale covers four domains of pleasure response: interest/pastimes, social interaction, sensory experience and food/drink (Snaith et al., 1995). The SHAPS is an accepted measure for measuring anhedonia in a range of populations including the general public, college students, and psychiatric patients (Leventhal et al., 2006; Snaith et al., 1995). It has demonstrated face, content and criterion validity, and is sensitive to differences between perceptible and clinically significant anhedonia, as well as to changes in clinical status (Snaith et al., 1995).

Drug Purchase Task. A drug purchase task will be used to assess economic demand for the sampling dose (Amlung et al., 2015; Bruner & Johnson, 2014; Murphy & MacKillop, 2006). In this task subjects are asked to indicate the hypothetical number of “hits” (i.e., the dose of drug they received during the sampling phase) they would purchase at a future date at monetary increments ranging from $0.00 (free) to $140/hit. All choices are hypothetical and will not be purchased or administered. Subjects will complete the Drug Purchase Task at 1330, approximately 4 hours after sample dose administration. The Drug Purchase Task is included in Appendix B.

Data Analyses:

Data will be analyzed as raw scores. Statistical significance refers to $p \leq 0.05$. Demographic data from the DUL cohorts (0, 60 mg/day) will be compared using t-tests. Variables for which the cohorts differ, if any, will be used as covariates in subsequent analyses. Physiological and subjective responses to intranasal MA from the medical safety session will also be analyzed to demonstrate that the DUL cohorts are comparable. Data will be analyzed as peak effect (i.e., maximum effect observed following each administration of intranasal MA) and AUC (calculated for each participant via the trapezoidal method) with mixed-model ANOVA with DUL cohort (0 or 60 mg/day) and MA (0, 10, 20 mg) as factors. A main effect of DUL cohort or a MA-DUL interaction will indicate that the cohorts responded differently to MA. MA self-administration (i.e., number of doses earned) will be analyzed with three-factor mixed-model ANOVA with MA (within-subject variable; 0, 10, 20 mg), DUL (between-subject variable; 0 or 60 mg/day) and MTH (within-subject variable; 0, 20, 40, 60 mg/day) as factors. A significant attenuation (i.e., rightward shift in the dose response) of the effects of MA will be inferred if the main effect of DUL or MTH, the MA-DUL interaction, the MA-MTH interaction, or the MA-DUL-MTH interaction attains statistical significance in the ANOVA. If the MA-DUL-MTH interaction attains statistical significance, the mean square error term will be used to conduct Tukey's HSD *post-hoc* test to make appropriate pair-wise comparisons between means. Number of doses earned on the MA self-administration procedure will be used to determine if the effects of the DUL-MTH combinations on self-administration of the MA doses are additive, supra-additive, or infra-additive (i.e., isobolographic analysis) (Grabovsky and Tallarida 2004; Tallarida, 2006; Wessinger, 1986; Woolverton, 1987). Number of doses earned (group mean, standard error) under a dose combination will be considered: 1) additive if it overlaps with the arithmetic sum of the effects observed under the DUL and MTH doses alone; 2) supra-additive if it is greater than the sum of the individual dose alone and without overlap; or 3) infra-additive if it is less than the sum of the effects of the individual doses alone and without overlap. Peak-effect and AUC data from the subjective-effects questionnaires and physiological measures following administration of the sampling dose will be calculated and analyzed in the same fashion as break point data. Physiological and subjective-effects data following self-administered MA will not be analyzed because participants will likely ingest varying amounts of MA. Data from the Attentional Bias-Behavioral Activation (i.e., proportion of inhibitory failures to no-go targets following MA go cues minus proportion of inhibitory failures to no-go targets following neutral cues), Hypothetical Delay Discounting (i.e., indifference points and AUC), and the Snaith-Hamilton Pleasure Scale (i.e., Composite Score) will be analyzed with two-factor mixed-model ANOVA with DUL (between-subject variable; 0, 60 mg/day) and MTH (within-subject variable; 0, 20, 40, 60 mg/day). A significant improvement will be inferred if the main effect of DUL or MTH, or the DUL-MTH interaction attains statistical significance. If the DUL-MTH interaction attains significance, the mean square error term will be used to conduct Tukey's HSD *post-hoc* test to make appropriate pair-wise comparisons between means. The primary outcome measure is the number of doses earned on the self-administration procedure by participants maintained on DUL-MTH combinations. We used the results of a previous study conducted in our laboratory to determine an appropriate sample size for the present experiment (Rush et al., 2018d). In a complete within-subject study, maintenance on NTX (50 mg/day) combined with oxazepam (40 mg/day) decreased MA (10 and 30 mg) self-administration relative to placebo-placebo maintenance with an average estimated effect size (Cohen's *d*) of 0.24. Considering the design of the proposed trial (i.e., two DUL cohorts [0 or 60 mg/day], four MTH maintenance conditions [0, 20, 40, 60 mg/day], and three doses of intranasal MA [0, 10, 20 mg]), enrolling 28 participants (i.e., 14/DUL cohort) will provide power to detect an effect size of 0.2 for attenuation of the reinforcing effects of MA as a function of maintenance on the DUL-MTH combinations relative to placebo maintenance as well as compared to the constituent compounds alone (power > 0.80, $\alpha = 0.05$, G*Power).

8. RESOURCES

This study will take place at the CCTS-IRU. Study sessions will only be conducted on weekdays. All drug administration will take place at the UK CCTS-IRU in a room equipped with all the necessary physiologic and computer equipment for the study. Dr. Hays is an adult psychiatrist who has worked extensively with individuals with substance use disorders in both the clinical and research setting and he is the responsible medical investigator for this study. Dr. Rayapati is a psychiatrist who has worked extensively with individuals with substance use disorders in both the clinical and research setting and he is the back up medical investigator for this study. They will be available to attend to medical problems as well as any psychological or psychiatric issues that may arise. Drs. Rush and Stoops will provide scientific oversight for the study and have safely completed numerous human behavioral pharmacology studies. Overall, the study team and resources described above are well equipped to protect subjects and successfully implement, carry out and complete this study protocol.

9. POTENTIAL RISKS

The subject-rated drug-effect questionnaires and physiological measures employed in these studies are benign. The risks to the study subjects are those related to the ingestion of the drugs under study. All of the drugs to be administered in the proposed research are commercially available. The relative safety as well as the contraindications and possible side effects of these compounds are well known and documented. However, the administration of any drug involves some risks simply because individuals differ in their reactions to drugs. The main risk is that subjects will experience side effects that may be unpleasant.

Side effects of MA include nausea, abdominal pain, loss of appetite, dry mouth, weight loss, changes in mood, headache, tremor, difficulty sleeping, nervousness, restlessness, increases in temperature, changes in heart rate or blood pressure (including irregular heart rate and blood pressure), palpitations, anxiety, dizziness, hallucinations, forgetfulness, sleepiness and performance impairment. The severity and likelihood of these side effects usually varies with dosage and chronic administration. More serious side effects could include allergic reaction, chest pain, heart attack or other heart related problems, changes in blood platelet levels, stroke, psychotic episodes, seizures, Tourette's Syndrome and sudden unexplained death. These side effects are associated with the self-administration of supratherapeutic doses of MA under unsupervised conditions. These side effects may be more frequent and larger in magnitude when testing the DUL-MTH-MA combinations.

Common side effects of MTH include anxiety, restlessness, diaphoresis, irritability, suppressed appetite, muscle twitching, insomnia, gastrointestinal upset, increased heart rate, increased blood pressure, palpitations, and arrhythmias. More serious side effects following the chronic, unsupervised administration of much higher doses of illicit psychomotor stimulants have occurred, and include psychotic episodes, decreased breathing, seizures, myocardial infarctions, heart failure, and death. These side effects may be more frequent and larger in magnitude when DUL and MTH are combined.
The doses to be administered in the present experiment were chosen to minimize, if not eliminate, the chance of these side effects occurring since these side effects are related to dose. Thus, it is unlikely that subjects will experience side effects during the experimental protocol. All experiments proposed in this application will be conducted at the CCTS-IRU and under medical supervision. Side effects of the drugs are temporary, usually dissipating in less than 24 hours. The principal investigator on this project, Dr. Rush, has had extensive experience for over 20 years administering therapeutic and supratherapeutic doses of stimulant drugs to subjects in an outpatient setting and has never observed untoward effects. Dr. Rush will train all staff on this project.

Common side effects of DUL include changes in vision, agitation, anxiety, body aches or pain, cough, dizziness/lightheadedness, constipation, diarrhea, difficulty with breathing, dry mouth, ear congestion, changes in urination, headache, fainting, increased blood pressure, weakness, loss of appetite, loss of voice, muscle aches, nausea, nervousness, rash, itchiness, changes in sexual function, sleepiness or unusual drowsiness, sleeplessness, sneezing, sore throat, swelling, stuffy or

runny nose, sweating, tremor and weight change. More serious side effects of DUL include angle-closure glaucoma, unusual bruising/bleeding, seizures, hallucinations, worsening of existing depression or suicidal thoughts and Stevens-Johnson syndrome.

To avoid potential drug interactions, subjects taking any prescribed medication chronically, except birth control, will be excluded. The medical personnel on this protocol will determine if it is safe for a potential subject to discontinue taking their medication during their participation.

There is some theoretical risk that subjects might choose to seek out illicit sources of drugs they received experimentally and liked. However, this risk is minimal since all drugs are administered under blind conditions and in a setting, that is not conducive to the development of dependence.

10. SAFETY PRECAUTIONS

Subjects are carefully screened (history and physical exam, routine labs such as CBC, complete metabolic panel and urinalysis, ECG and psychiatric assessment) to exclude those with potential increased risk of adverse effects, such as personal or family histories of heart disease, histories of seizure or head injury associated with more than a brief loss of consciousness, hypertension, psychosis, etc. During sessions subjects remain under careful medical observation and are monitored continuously by on-site medical staff. Vital signs will be collected throughout the dosing period. Staff is familiar with the acceptable physiological parameters for these studies and this information is posted in every experimental session room. In addition, Dr. Rush has substantial experience administering medications to human subjects under a variety of dosing conditions. Lastly, female subjects are also given pregnancy tests prior to each session to ensure that we do not administer active medications to a pregnant woman.

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

11. BENEFIT vs. RISK

The degree of risk to which individual study subjects are exposed as a consequence of their research participation is slight. In contrast, the potential and probable benefits to be derived by society in general and by patients as a group appear to be considerable. The major benefits of these studies are clinical and scientific ones related to the knowledge gained about putative medications for methamphetamine use disorders. The data from this project will contribute to a better understanding of drug abuse and will ultimately contribute to the development of improved prevention, control and treatment procedures. Individual study subjects are expected to benefit personally from the financial payments that are provided for their research participation, from the medical and psychiatric evaluations and from referrals for medical and psychiatric treatment that are provided whenever appropriate. Overall, the risk/benefit ratio appears favorable and the conduct of this research seems well justified.

12. AVAILABLE ALTERNATIVE TREATMENTS

There are no available alternative treatments as this is not a treatment study. If subjects express the desire for treatment they will be given referrals for treatment and not be allowed to participate in this study.

13. RESEARCH MATERIALS, RECORDS AND PRIVACY

Urine and blood samples will be collected at screening prior to a subject's participation in the experimental protocol under another IRB approved protocol (# 44379). These urine samples will be tested for the presence of a full range of drugs of abuse. Blood samples will be used for the laboratory chemistries. Females will also be given a pregnancy test at the time of screening (via the urine

sample). Urine drug and pregnancy tests will be conducted prior to the conduct of each experimental session. Other data obtained from the subjects will involve subjective effects based on questionnaires, various computer-based tasks and non-intrusive staff observations and ratings. The consent form states that subject's confidentiality will be protected.

14. CONFIDENTIALITY

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

15. PAYMENT

Participants will be paid $50 for each day they reside on the CCTS-IRU and will receive a $50 completion allowance for these days if they complete the entire experiment. The amount earned by the subject will be disbursed to them upon completion of the study. Additionally, Participants will earn $50 at both of the follow-up visits scheduled 1- and 2-weeks after discharge. Payments will be disbursed in amounts up to $500 dollars and will be given once per week following discharge until the subject is paid in full. When subjects return on a weekly basis to receive their payments, we will survey them regarding their drug use since being discharged from the study. A subject can earn approximately $3300 for participating in the study.

16. COSTS TO SUBJECTS

There will be no cost to the subject for participating. Costs for the screening procedures (i.e., medical history questionnaire, physical examination including laboratory chemistries (blood chemistry screen, complete blood count, urinalysis) and a psychiatric examination will be paid by the Laboratory of Human Behavioral Pharmacology.

17. DATA AND SAFETY MONITORING

Data Monitoring Plan

Data will be collected using a computerized data collection and management system wherever possible. This system automates the collection of data, which ensures the accuracy and completeness of data collection. The data are stored in a unique file on the hard drive of the computer and are printed after all the tasks are completed. In all instances, the data files do not contain the name of the subject, but instead, each subject is identified by a unique four-digit number. A computer file linking the unique number with the subject's name will be kept on a stand-alone, password-protected computer. All data requiring hand entry (e.g., cardiovascular measures) will be entered by two separate staff members and comparison macros will be run to ensure accuracy. Data files for experimental tasks and physiological measures from each experimental session will be manipulated and combined into a single electronic spreadsheet for each subject by one of the investigators. Data for all subjects will then be combined into a single electronic spreadsheet and separated by experimental measure for statistical analysis using SPSS (IBM, Armonk, NY). The primary outcome measure will be the influence of DUL-MTH maintenance on the reinforcing effects of MA. The alpha level will be set at 5%.

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

Safety Monitoring Plan

Potential participants will provide information regarding their drug use history and undergo an extensive physical and psychiatric health screening to determine their eligibility and safety of their participation. Any potential subject with a history of clinically significant physical disease, current physical disease (e.g., impaired cardiovascular functioning, histories of seizure, head trauma or CNS tumors) or current or past histories of psychiatric disorder that in the opinion of the study physician would interfere with study participation, other than substance abuse or dependence, will be excluded from research participation. Females must be using an effective form of birth control in order to participate and must not be pregnant. Males must also be using an effective form of birth control in order to participate. Methods for monitoring adverse events (AEs) will include observations by the medical and research staff, spontaneous report by the subjects and, regular measurement of cardiovascular function. Participants will not receive study drug if they have any signs or symptoms that may contraindicate its administration (e.g., HR and BP outside of predetermined range, development of serious side effects).

All AEs occurring during the course of the study will be collected, documented and reported to the PI. The occurrence of AEs will be assessed for the duration of participation. Each week a study investigator will review the AE forms from the previous week for events that were reported as new or continuing. The study investigators will follow all AEs to the point of a satisfactory resolution. Subjects may be withdrawn from the study if the medically responsible investigator determines it is the best decision in order to protect the safety of the subject. All AEs will be assessed to determine if they meet criteria for a serious adverse event (SAE).

Serious adverse events, as defined by the Food and Drug Administration (FDA), will be systematically evaluated for the duration of participation and during the follow-up visits at 2- and 4-weeks following study completion. Any SAE, whether or not related to the study drug, will be reported to the IRB, CCTS-IRU, NIDA and the FDA. The initial SAE report will be followed by submission of a completed SAE report to all three institutions.

In the event that a subject either withdraws from the study or the investigator decides to discontinue a subject due to an SAE, the subject will have appropriate follow-up medical monitoring. Monitoring will continue until the problem requiring hospitalization has resolved or stabilized with no further change expected, is clearly unrelated to the study drugs or results in death. Outcome of SAEs will be periodically reported to IRB, CCTS-IRU, NIDA, and the FDA. A summary of the SAEs that occurred during the previous year will be included in the annual progress report to NIDA, the IRB, CCTS-IRU, and FDA.

Data and Safety Monitoring Board (DSMB)

An independent DSMB will be formed and used for this study. For this investigator-initiated protocol, the DSMB will be

- Catherine A. Martin, MD, (Chair)
- Hannah Knudsen, Ph.D. (member);
- Shanna Babalonis, Ph.D. (member); and
- Amy Atkerson (Executive Secretary).

Other members (e.g., bioethicist) will be recruited as needed.

During the initial meeting, the DSMB will approve the initiation of the proposed experiment. This approval will be based on review of the research protocol, informed consent documents, and plans for data safety and monitoring.

Subsequent meetings of DSMB will occur at least annually. Additional meetings will be scheduled if warranted by the volume of activity, adverse events or new information pertaining to the protocol. These meetings may be called ad hoc by the chairperson of the DSMB, Dr. Cathy A. Martin. The DSMB meeting for this protocol will only be considered to take place if all members of the DSMB

are present. The initial DSMB meeting may occur earlier than after the initial quarter than the protocol is approved. The chairperson may halt a study until review by the DSMB.

For subsequent meetings, the PI for the protocol will submit a DSMB report to the chairperson prior to the DSMB meeting. The DSMB report will:

1) Briefly review the protocol's DSM plan.

2) Report and review all adverse events. These will include a summary of the frequency and severity of adverse events and address the question of whether or not the protocol should continue in light of the adverse events. The reasons for any study dropout will also be included.

3) Any new information (published or unpublished data, etc.) which may alter the risk/benefit ratios for the study. The underlying principle is that no further risk of research subjects is justified if the hypothesis has been disproved.

4) A statement regarding whether or not the study should be modified or terminated because of toxicity or safety reasons. If modifications are needed, then the specific proposed modifications should be included.

5) The total number of patients enrolled and whether or not all entry criteria for the protocol were met. Any protocol violations or other problems related to DSM should be noted, and it should specifically be stated if there are none.

The DSMB report will be discussed at the DSMB meeting first in an open session in which the PI may be present to address any questions raised by the DSMB. There will also be a closed session in which the report will be discussed and amended as necessary. The DSMB must present a motion as to whether or not the DSM report is acceptable as amended and whether or not the study should be allowed to continue as well as the next planned DSMB meeting for review of the DSM report. The final DSMB report will be forwarded to the PI, the IRB chairperson and the NIDA Program Officer.

If the study is halted, the PI has the right to formally appeal the DSMB. If a study is halted, the IRB, NIH, FDA, or other appropriate regulatory agencies will be notified. The chairperson will maintain a log of DSM reports and actions taken pertaining to them.

The DSM mechanisms do not in anyway relieve the PI of the primary responsibility of reporting serious or unexpected adverse events and deaths related to the protocol to the IRB, FDA or NIH. In addition, these mechanisms in no way can be construed as replacing or minimizing the primary role of the IRB in reviewing adverse events and meeting their statutory responsibilities.

18. SUBJECT COMPLAINTS

Participants may at any time ask study personnel questions about the study procedures or make complaints. All staff will be aware to notify Drs. Rush, Stoops, Lile, Hays, or Rayapati about any subject concern or complaint as it arises. Participants will be allowed the opportunity to discuss any concerns or questions with an investigator promptly, in person and in confidence. It should be noted, however, that subjects will be told that some concerns and complaints will not be kept private such as an adverse event, protocol deviation or threat to the safety of subjects or integrity of the research study. In these cases, all information will be made available to the Principal Investigator in order to determine any further course of action. Dr. Hays or Rayapati will also communicate with the nursing or laboratory staff on at least a weekly basis in order to discuss any concerns regarding particular subjects or with respect to the conduct of the study.

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

20. HIV/AIDS RESEARCH POLICY Not applicable.

21. PI SPONSORED FDA-Regulated Research

Dr. Rush holds an Investigational New Drug (IND) for intranasal MA. This application will be modified to combining methamphetamine with oral DUL and MTH. Dr. Rush has held INDs for behavioral pharmacology research with a number of drugs for over ten years and is well aware of the necessary reporting requirements and other responsibilities associate with IND sponsorship. As required by the FDA, Dr. Rush will submit annual reports on the progress of the IND and will also report serious adverse events in accordance with published guidelines. Dr. Rush has trained all study staff on their responsibilities regarding the IND.

Combined Consent and Authorization to Participate in a Research Study

KEY INFORMATION FOR BEHAVIORAL EFFECTS OF DRUGS: INPATIENT (40)

You are being invited to take part in a research study about the effects of drugs on behavior. You are being asked to participate because you are 18-55 years old with a recent history of stimulant use. You are also being asked to participate because you have expressed interest in participating in this study, you passed the medical screen and it is unlikely that you will react badly to the laboratory setting or to the drugs you will take.

WHAT IS THE PURPOSE, PROCEDURES, AND DURATION OF THIS STUDY?

This medication development experiment is testing the effects of methylphenidate (a medication used to treat Attention Deficit Hyperactivity Disorder [ADHD]), duloxetine (a medication used to treat depression) and their combination on the subjective and physiological effects of methamphetamine. We are also interested in determining whether methylphenidate, duloxetine or their combination impacts whether you like the drug and want to take it again. The prescription drugs to be administered in the study are approved by the Food and Drug Administration but not for the proposed use.

Your participation in this research will last about one month. The research procedures will be conducted in the Center for Clinical and Translational Services Inpatient Research Unit (CCTS-IRU) at the University of Kentucky Medical Center. During the time you participate, you must agree to participate as an inpatient on the CCTS-IRU. You will be asked to reside on the CCTS-IRU over approximately one month and complete 1 practice session, 1 medical safety session and 12 experimental session days.

The purpose of this research is to gather information on the safety and effectiveness of methylphenidate, duloxetine, and their combination on the behavioral, subjective and physiological effects of methamphetamine.

WHAT ARE REASONS YOU MIGHT CHOOSE TO VOLUNTEER FOR THIS STUDY?

Understand that you are not a patient receiving medical treatment and that you will not receive any direct benefits from this study. However, the knowledge gained will contribute to a better understanding of the nature of effects of these drugs and may result in improved therapeutic treatments for patients taking these drugs. If you are seeking treatment, please notify the investigator now and he will make the necessary referral. For a complete description of benefits, refer to the Detailed Consent.

WHAT ARE REASONS YOU MIGHT CHOOSE NOT TO VOLUNTEER FOR THIS STUDY?

The primary risks to participation are those specifically related to the ingestion of the study drugs. Two types of risk are associated with the administration of these drugs to human volunteers. First, the drugs under study occasionally produce side effects. Second, there is a slight risk that habituation or tolerance will develop. If you develop habituation or tolerance to the medications administered in the study, the effects of these medications would be decreased if they were administered to you at therapeutic doses. For a complete description of risks, refer to the Detailed Consent.

If you do not want to be in the study, there are no other choices except not to take part in the study.

DO YOU HAVE TO TAKE PART IN THE STUDY?

If you decide to take part in the study, it should be because you really want to volunteer. You will not lose any services, benefits or rights you would normally have if you choose not to volunteer.

WHAT IF YOU HAVE QUESTIONS, SUGGESTIONS OR CONCERNS?

The person in charge of this study is Craig R. Rush, Ph.D of the University of Kentucky, Departments of Behavioral Science, Psychiatry, and Psychology. If you have questions, suggestions, or concerns regarding this study or you want to withdraw from the study his/her contact information is: 859-257-5388

If you have any questions, suggestions or concerns about your rights as a volunteer in this research, contact staff in the University of Kentucky (UK) Office of Research Integrity (ORI) between the business hours of 8am and 5pm EST, Monday-Friday at 859-257-9428 or toll free at 1-866-400-9428.

DETAILED CONSENT:

ARE THERE REASONS WHY YOU WOULD NOT QUALIFY FOR THIS STUDY?

You should not participate if you have a history of serious physical disease, current physical disease, impaired cardiovascular functioning, high blood pressure, chronic obstructive pulmonary disease, history of epilepsy or seizure, diabetes, current or past histories of serious psychiatric disorder. You should not participate if you have a history of other significant medical problems.

You should not participate if you are seeking treatment for your drug use, are currently in treatment for your drug use, or are currently in successful remission from your drug use. If you have ever been addicted to drugs or alcohol, you should discuss this with the research staff before agreeing to participate.

If you are a female, you should not participate if you are pregnant or plan on becoming pregnant during your participation in this experiment. You must be using an effective form of birth control (e.g. birth control pills, surgically sterilized, IUD, cervical cap with a spermicide, condoms or abstinence), and you must be willing to take a pregnancy test before being accepted into the research study. You will also be required to take a pregnancy test prior to each experimental session. Should one of these tests show that you are pregnant, your participation will be terminated immediately. If you are female, you should not participate if you are lactating or breast feeding a baby.

If you are male, you must be using an effective form of birth control (e.g., condoms with spermicidal lubricant, surgically sterilized, or abstinence), before being accepted in the research study and during the research study. Failure to the birth control instructions listed above will result in immediate termination of your participation.

Both female and male participants are advised to continue using birth control methods following discharge from the study, whether you complete the study in its entirety or not. This advisement is due to the time needed to for your body eliminate or breakdown duloxetine following study participation and the taper dosing during post-discharge.

WHERE IS THE STUDY GOING TO TAKE PLACE AND HOW LONG WILL IT LAST?

The research procedures will be conducted in the CCTS-IRU at the University of Kentucky Medical Center. During the time you participate, you must agree to participate as an inpatient on the CCTS-IRU. You will be asked to reside on the CCTS-IRU over approximately one month and complete 1 practice session, 1 medical safety session and 12 experimental session days. You must agree to follow the general rules of the CCTS-IRU and share in the routine responsibilities of keeping the unit and yourself neat, clean and orderly. You will be provided a detailed list of the CCTS-IRU rules before being admitted as an inpatient. You should understand that during the time that you spend on the CCTS-IRU that you will not be allowed to leave the unit unsupervised, nor will you be allowed to have visitors. You will be allowed to make telephone calls.

WHAT WILL YOU BE ASKED TO DO?

Before participating in this research study, it will be necessary for you to have a physical and psychiatric examination. During the time you participate, you must agree to participate as an inpatient on the CCTS-IRU for approximately one month or until we successfully complete up to a maximum of 14 sessions. During the time you participate, you must abstain from using any illicit substances, alcohol, and caffeine. The first session day will be a “practice” session day to make you familiar with the various tasks and procedures of the experiment. The second session will be a medical safety session to ensure you tolerate the intranasal drug. The remaining experimental sessions will occur in blocks of 3 sessions approximately 4 days apart while you reside on the CCTS-IRU. Session days will last approximately 6 hours each. During the sessions, we will collect data concerning your physiological status, your subjective status and your performance on various laboratory tasks. That is, we will record your heart rate, blood pressure, and temperature. We will also repeatedly ask you to answer various questionnaires about how you feel and about what kind of drug effect you feel and ask you to complete measures of hand eye coordination or response time. Finally, you will also have the opportunity to work to receive the drug you sampled in some sessions. The scheduled tasks pose no hazard or risk to you. You must agree to complete these forms and to do the tasks to the best of your ability and at the

scheduled times. On the days that you are not participating in a session, you will be free to engage in approved recreational activities (for example, television, reading material, music, arts and crafts, video games or board games).

During your participation, you must not use any drug except those administered in the experiment. There will be urine checks, breathalyzers and room-searches on a random schedule for evidence of unauthorized drug or alcohol use. If a urine screen or breathalyzer shows that you used other drugs or alcohol or you have them in your possession, you will be dropped from the study. If you are dropped from the study because you used other drugs or alcohol, or had them in your possession, your participation would end and you will only receive payment for the days and experimental sessions you completed.

You should also understand that during the time that you spend on the CCTS-IRU we will provide you with standard hospital meals that are **caffeine free**. You will not be permitted to drink caffeinated beverages (coffee, soft drinks other than those that are decaffeinated) during the month you are in the CCTS-IRU. When you are not participating in experimental sessions, we will provide you with recreational activities (television, reading material, music, arts and crafts, video games or board games). For your enjoyment, you will be allowed to use certain items that we purchase. These items may include, but are not limited to, portable radios, video movies and games, puzzles, games, books, and magazines. We would also like to especially encourage you to use some of the educational software that we have purchased. If you use any of these materials, and do not return them or ruin them, you should understand the price of the item will be deducted from your payment. When you come to the CCTS-IRU, you should not bring any valuable items with you.

Daily experimental procedures. On your admission day, you will arrive at the Laboratory of Human Behavioral Pharmacology at 8:00 AM. We will then conduct a urine drug screen and field sobriety test. If you pass the urine screen and the field test, at approximately 9:00 AM you will be escorted to the CCTS-IRU, where you will be admitted. On your second day, you will complete a "practice" session. This practice session is to familiarize you with the experimental routine, although you will not receive any medication on this day. On your third day, you will complete a medical safety session to ensure you tolerate the intranasal drug well. On the day following your medical safety session, you will begin taking capsules orally once daily. Approximately 4 days following the beginning of capsule administration, you will complete 3 experimental session days and then complete three more sets of 3 session days approximately every 4 days after that. There will be a total of 12 experimental sessions. The experimental session will be approximately 7 hours long. You should understand that you will not be allowed to smoke during the experimental session which will last approximately 7 hours. You will be discharged from the CCTS-IRU on the day following your last experimental session. We have included a table in the Appendix to help you better understand the study protocol. This table is meant to serve as an example. In order to avoid conducting experimental sessions on weekend days (Saturday and Sunday), your stay may be extended by at least 6 days. Thus, your participation may be longer than 32 days. After you are discharged from the study, you will come in weekly to receive remaining payments in increments of up to $500. At that time, you will also complete a basic follow up in which we will ask you about your drug use, measure your heart rate and blood pressure and test your urine for the presence of drugs.

Drugs and Drug Administration. During the experiment, you will be given doses of commonly prescribed drugs or illicit drugs. Drugs will be administered by mouth or through your nose. The drugs tested will be placebo (a blank, no drug), an ADHD medication (methylphenidate [Metadate CD®]), an anti-depressant (duloxetine [Cymbalta®]) and methamphetamine. This combination of drugs is experimental.

The prescription drugs will be administered in doses approved by the Food and Drug Administration (FDA). These drugs will be administered alone and in combination.

WHAT ARE THE POSSIBLE RISKS AND DISCOMFORTS?

The laboratory tasks and subjective-effects questionnaires present no risks exceeding those of everyday experience. The primary risks to participation are those specifically related to the ingestion of the study drugs. Two types of risk are associated with the administration of these drugs to human volunteers. First, the drugs under study occasionally produce side effects. These are outlined in the

Appendix. We will monitor for these side effects daily while you reside on the CCTS-IRU. If you feel you are experiencing any of these side effects, you should tell the nursing staff or physician. In addition, study participation may involve risks that are currently unforeseeable. **You should understand that the combination of the drugs administered in the study may increase the frequency or severity of drug side effects.**

Second, there is a slight risk that habituation or tolerance (i.e., decrease in the effect) will develop. If you develop habituation or tolerance to the medications administered in the study, the effects of these medications would be decreased if they were administered to you at doses a doctor would prescribe.

Some medications administered in this study have been linked to rare reports of sudden death. Patients taking this medication that have died most often had undiagnosed personal heart related problems or a family history of heart problems. **We will screen you for heart problems using an electrocardiogram and by screening both you and your immediate family's medical history. You should NOT participate in this research if you know of any heart related problems for yourself or your immediate family.**

This is always a chance that any research can harm you. The research procedures in this study are no different. In addition to the risks described in this consent, you may experience a previously unknown risk or side effect.

WILL YOU BENEFIT FROM TAKING PART IN THIS STUDY?

Understand that you are not a patient receiving medical treatment and that you will not receive any direct benefits from this study. However, the knowledge gained will contribute to a better understanding of the nature of effects of these drugs and may result in improved therapeutic treatments for patients taking these drugs. If you are seeking treatment, please notify the investigator now and he will make the necessary referral.

WHAT WILL IT COST YOU TO PARTICIPATE?

Participating in this research study will not cost you anything. The clinical laboratory tests, physical examination and psychiatric screen described above will be paid by a grant from the National Institute on Drug Abuse (NIDA).

You and/or your insurance company, Medicare or Medicaid will be responsible for the costs of all care and treatment you receive during this study that you would normally receive for your condition. These are costs that are considered medically reasonable and necessary and will be part of the care you receive if you do not take part in this study.

WHO WILL SEE THE INFORMATION THAT YOU GIVE?

Every effort will be made to maintain the confidentiality of your study records. The data from the study may be published; however, you will not be identified by name. Your identity will remain confidential, unless you give prior written approval or unless disclosure is required by law. Your name, address and social security number will be listed on the receipt for payment that you receive, as required by the Internal Revenue Service; but no information about your participation in this research project will be released. We will be collecting your social security number for payment purposes. You cannot participate in this research if you withhold your social security number.

To ensure the study is conducted properly, Officials of the Food and Drug Administration, the National Institutes of Health, and the University of Kentucky may look at or copy pertinent portions of records that identify you.

CERTIFICATES OF CONFIDENTIALITY

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. The researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases but

not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings, see below); if you have consented to the disclosure, including for your medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research subjects.

The Certificate cannot be used to refuse a request for information from personnel of the United States federal or state government agency sponsoring the project that is needed for auditing or program evaluation by National Institute of Health (NIH) which is funding this project or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA). You should understand that a Certificate of Confidentiality does not prevent you from voluntarily releasing information about yourself or your involvement in this research. If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow the researchers to release it.

Again, to help us protect your privacy, this research has a Certificate of Confidentiality. The researchers can use this Certificate to refuse to disclose information that may identify you to anyone not connected with this study, or in any legal proceedings. The exceptions to this rule are release of information:

- you have requested us to provide, for instance, to your insurance company or doctor;
- to the sponsor (e.g., National Institutes of Health) or agency auditing the research (e.g., Food and Drug Administration);
- about child or elder abuse, neglect, or harm to yourself or others; and
- about you if it involves a reportable disease.

This policy does not prevent you from releasing information about your own participation in this study.

CAN YOU CHOOSE TO WITHDRAW FROM THE STUDY EARLY?

You can discontinue your participation in this study at any time. If you choose to withdraw from the study, you will be required to remain in the facility until the investigators are satisfied that you are no longer affected by the drug. During this time, you will be free to spend your time engaged in activities that are not part of the study. You should understand that you must remain in the facility in order to protect yourself and others from the effects of the drug and that your judgment while you are affected by the drug may be impaired sufficiently to necessitate that you remain in the facility. If you choose to leave the study early, data collected until that point will remain in the study databases and may not be removed.

You should understand, however, that if you decide to withdraw from the study early you will not receive any of the completion allowance described below. You will receive the $50 per session completion allowance for each of the experimental sessions you completed and the amount of groceries equal to the value of the vouchers you receive for the experimental sessions you completed.
You should understand the principal investigator on this project, Craig R. Rush Ph.D., can terminate your participation for the following reasons: 1) failure to adhere to patients rules for CCTS-IRU, 2) if you verbally or physically assault another volunteer, patient or staff member on the CCTS-IRU, 3) if your behavior is disruptive to other ongoing studies that are conducted on the CCTS-IRU, 4) if your behavior is disruptive to the other volunteers, patients, research staff or medical staff on the CCTS-IRU, 5) failure to comply with the alcohol, drug, and food restrictions, 6) failure to comply with the pregnancy restrictions, 7) failure to complete a scheduled experimental session, 8) failure to perform the behavioral tasks to the best of your ability, 9) if you leave the hospital against the advice of the principal investigator or the medical doctors. If you are terminated for any of these reasons, it will be deemed that you did not complete all of your scheduled experimental sessions and you will not receive the completion allowance described below.

You should also understand that the medical doctors on this project, Lon R. Hays, MD, M.B.A. and Abner O. Rayapati, M.D., can terminate your participation if they do not feel that it is medically safe for you to continue. If your participation is terminated for medical reasons, you will receive the $50/session completion allowance for each of the experimental sessions you completed.

ARE YOU PARTICIPATING, OR CAN YOU PARTICIPATE, IN ANOTHER RESEARCH STUDY AT THE SAME TIME AS PARTICIPATING IN THIS ONE?

You may not take part in this study if you are currently involved in another research study. It is important to let the investigator/your doctor know if you are in another research study. You should also discuss with the investigator before you agree to participate in another research study while you are enrolled in this study.

WHAT HAPPENS IF YOU GET HURT OR SICK DURING THE STUDY?

If you believe you are hurt or if you get sick because of something that is due to the study, you should call Lon R. Hays, M.D., M.B.A. at (859) 323-6021 x 79015 or Abner O. Rayapati, M.D. at (859) 257-9175 immediately. You can also call 911 in the case of an emergency. Dr. Hays or Dr. Rayapati will determine what type of treatment, if any, is best for you at that time. The medical costs related to your care and treatment because of research related harm will be your responsibility.

It is important for you to understand that the University of Kentucky does not have funds set aside to pay for the cost of any care or treatment that might be necessary because you get hurt or sick while taking part in this study. Also, the University of Kentucky will not pay for any wages you may lose if you are harmed by this study.

The medical costs related to your care and treatment because of research related harm will be your responsibility.

You do not give up your legal rights by signing this form.

WILL YOU RECEIVE ANY REWARDS FOR TAKING PART IN THIS STUDY?

You will be paid for your participation in this experiment. You will earn $50 for each day that you reside on the CCTS-IRU. If you complete all of your scheduled experimental sessions, you will be paid a completion allowance of up to $50 for each of the days you resided at the CCTS-IRU. You will also receive $50 for the first two post-study follow up appointments that you attend. If you complete the entire study you may earn approximately $3,300.

You should understand that if you make more than a total of $600 by participating in research projects, the University of Kentucky will report your earnings to the appropriate state and federal government agencies (i.e., Internal Revenue Service [IRS]). You should further understand that it is your responsibility to determine how these earnings might affect your personal financial situation.

You should also understand that your earnings will be given to you in a series of separate payments. The first payment will be given to you on the day of your discharge. The remaining payments will be given to you once per week following your discharge. Due to University of Kentucky accounting policies, checks cannot be written for more than $500, so your payments will be given to you in amounts of up to $500 until you have received all of the money you are owed. For example, if you resided on the CCTS-IRU for 32 days and completed all experimental sessions and the first two follow-up appointment you would earn a total of $3300. Your first and remaining payments would be for up to $500 and would be given to you on the day you leave the CCTS-IRU and every week there after until you have received all of the money you have earned. When you come back for your payments, we will survey you about your drug use since we last saw you. <u>You will also need to provide a breath sample negative for alcohol when you return for your payments.</u> If you come to the LHBP with a breath sample positive for alcohol, your payment will be withheld until you can provide a breath sample negative for alcohol. We will not pay you additional money (other than the portion of the completion bonus you are receiving) when you come back for your payments and provide this information.

WHAT IF NEW INFORMATION IS LEARNED DURING THE STUDY THAT MIGHT AFFECT YOUR DECISION TO PARTICIPATE?

If the investigators on this project, Craig R. Rush, Ph.D., William W. Stoops, Ph.D., Lon R. Hays, MD, M.B.A. and Abner O. Rayapati, M.D. learn of new information in regards to this study, and it might change your willingness to stay in this study, the information will be provided to you. You may be asked to sign a new informed consent form if the information is provided to you after you have joined the study. If you choose not to continue, you will not lose any of your earnings. That is, you will receive the completion allowance for each of the experimental sessions you completed.

WILL YOU BE GIVEN INDIVIDUAL RESULTS FROM THE RESEARCH TESTS?

Do you give permission for Craig R. Rush, Ph.D. to contact you with information about research results or incidental findings that are determined to be important to you/your family's health? (Incidental findings are unforeseen findings discovered during the course of the research that may affect you or your family's health).

☐ Yes
☐ No _____Initials

You may also withdraw your consent to be contacted with information about research results or incidental findings by sending a written request to Craig R. Rush, Ph.D. 465 E. High Street, Suite 204B, Lexington, KY 40507.

WHAT ELSE DO YOU NEED TO KNOW?

If you volunteer to take part in this study, you will be one of about 28 people to do so. This research is supported by a grant from the National Institute on Drug Abuse (NIDA [DA R01DA047391]).

The privacy law, HIPAA (Health Insurance Portability and Accountability Act), requires researchers to protect your health information. This form describes how researchers may use your information. Please read it carefully.

Your health information will be used and/or released (disclosed) for the following research study: Behavioral Effects of Drugs (Inpatient): 40 (Methamphetamine, Methylphenidate and Duloxetine).

You allow Craig R. Rush, Ph.D. and his research staff at the University of Kentucky to create, access, use and release your health information for the purposes listed below.

A description of this clinical trial will be available on ClinicalTrials.gov as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

Your health information that may be used and released includes:

- Demographic information (for example, information about your race, gender, socioeconomic status, and age) related to this study.
- Results of physical examinations related to this study.
- Results of psychiatric screening tests related to this study.
- Results of questionnaires and study procedures related to this study.
- Results of blood tests and urine screens related to this study.
- Medical history related to this study.

Your health information will be used for:

- A study coordinated by Craig R. Rush, Ph.D. examining the effects of stimulant drugs. Your protected health information is necessary to conduct this line of research, as well as to meet legal, institutional, and accreditation requirements.

The Researchers may use and share your health information with:

- The University of Kentucky's Institutional Review Board/Office of Research Integrity,
- University of Kentucky Medical Center, Investigational Drug Service, CCTS, CCTS-IRU, and Clinical Research Organization,
- The National Institute on Drug Abuse,
- The Food and Drug Administration

The researchers agree to only share your health information with the people listed in this document.

Should your health information be released to anyone that is not regulated by the privacy law, your health information may be shared with others without your permission; however, the use of your health information would still be regulated by applicable federal and state laws.

You will not be allowed to participate in the research study if you do not sign this form. If you decide not to sign the form, it will not affect your:

- Current or future healthcare at the University of Kentucky
- Current or future payments to the University of Kentucky
- Ability to enroll in any health plans (if applicable)
- Eligibility for benefits (if applicable)

After signing the form, you can change your mind and NOT let the researcher(s) release or use your health information (revoke the Authorization). If your revoke the authorization:

- You will send a written letter to: Craig R. Rush, Ph.D. 465 E. High Street, Suite 204B, Lexington, KY 40507 to inform him of your decision.
- Researchers may use and release your health information already collected for this research study.
- Your protected health information may still be used and released should you have a bad reaction (adverse event).
- You will not be allowed to participate in the study.

If you have not already received a copy of the Privacy Notice, you may request one. If you have any questions about your privacy rights, you should contact the University of Kentucky's Privacy Officer between the business hours of 8am and 5pm EST, Monday-Friday at (859) 323-1184.

Appendix: Study Visits/Procedures

WHAT WILL YOU BE ASKED TO DO?

Day	Experimental Procedures
1	Admission to CCTS-IRU.
2	Practice Session.
3	Medical Safety Session. During this session, you will receive repeated doses of intranasal drug and will complete questionnaires, tasks and physiological measures.
4 – 31	Drug maintenance. Dosing will occur at approximately 0700.
8 – 10	Experimental sessions. These days will be divided into sampling and self-administration sessions. During these days you will also complete a number of questionnaires, tasks and physiological measures.
15 – 17	Experimental sessions. These days will be divided into sampling and self-administration sessions. During these days you will also complete a number of questionnaires, tasks and physiological measures.
22 – 24	Experimental sessions. These days will be divided into sampling and self-administration sessions. During these days you will also complete a number of questionnaires, tasks and physiological measures.
29 – 31	Experimental sessions. These days will be divided into sampling and self-administration sessions. During these days you will also complete a number of questionnaires, tasks and physiological measures.
32	Discharge and taper medication received.
Weekly After Discharge Until You Receive Your Full Payment	Payment and follow up.
Note	During your participation, we will not conduct experimental sessions on weekends. You will receive maintenance doses on weekends. In order to avoid experimental sessions on weekends, your stay may be extended by up to six days (i.e., three sets of weekend days).

Appendix: Risks

WHAT ARE THE POSSIBLE RISKS AND DISCOMFORTS?

Possible isk or side effect of methamphetamine	How often has it occurred?	How serious is it?	Can it be corrected?
nausea, abdominal pain, loss of appetite, dry mouth, weight loss, changes in mood, headache, tremor, difficulty sleeping, nervousness, restlessness, increases in temperature, changes in heart rate or blood pressure, palpitations, anxiety, dizziness, hallucinations, forgetfulness, performance impairment,	These can occur occasionally.	Somewhat serious	These side effects are likely to decrease over time as the medications clear from your system.
allergic reaction, chest pain, seizures, change in blood platelets, psychotic episodes, Tourette's Syndrome,	These are uncommon.	Serious	These may go away with treatment.
heart attack or other heart problems, sudden unexplained death	These are uncommon.	Very Serious	No

Possible risk or side effect of methylphenidate	How often has it Occurred?	How serious is it?	Can it be corrected?
anxiety, restlessness, difficulty sleeping, loss of appetite, changes in heart rate, dizziness, faintness, irritability, shaking, nausea or other gastrointestinal discomfort, headache, increased blood pressure, performance impairment, flushing and sweating	These are likely to or will occur.	Somewhat serious.	These side effects are likely to decrease over time as the medications clear from your system.
heart attack, stroke, psychotic episodes, seizure, death	These are extremely uncommon.	Very Serious	No

Possible risk or side effect of duloxetine	How often has it occurred?	How serious is it?	Can it be corrected?
changes in vision, agitation, anxiety, body aches or pain, cough, dizziness/lightheadedness, constipation, diarrhea, difficulty with breathing, dry mouth, ear congestion, changes in urination, headache, fainting, increased blood pressure, weakness, loss of appetite, loss of voice, muscle aches, nausea, nervousness, rash, itchiness, changes in sexual function, sleepiness or unusual drowsiness, sleeplessness, sneezing, sore throat, swelling, stuffy or runny nose, sweating, tremor and weight change	These commonly occur.	Somewhat serious	These side effects are likely to decrease over time as the medications clear from your system.
angle-closure glaucoma, unusual bruising/bleeding, seizures, hallucinations, worsening of existing depression or suicidal thoughts and Stevens-Johnson syndrome.	These are extreme-ly uncommon.	Very serious	These may go away with treatment.

INFORMED CONSENT SIGNATURE PAGE

You are a participant or are authorized to act on behalf of the participant. This consent includes the following:

- **Key Information Page**
- **Detailed Consent**
- **Appendices**

You will receive a copy of this consent form after it has been signed.

_____ _____
Signature of research subject, **Date**

_____
Printed name of research subject

_____ _____
Printed name of [authorized] person obtaining informed consent/HIPAA authorization Date

_____
Signature of Principal Investigator or Sub/Co-Investigator