NIDA PROTOCOL

PHASE 1, DOUBLE-BLIND, PLACEBO-CONTROLLED ASSESSMENT OF INTERACTIONS BETWEEN 2 DOSES OF COCAINE AND THREE DOSES OF ESCALATING GBR 12909 IN COCAINE USING VOLUNTEERS

CONDUCTED AT

UNIVERSITY OF TEXAS MEDICAL BRANCH-GALVESTON
GENERAL CLINCIAL RESEARCH CENTER
BY UTMB PHARMACOLOGY &
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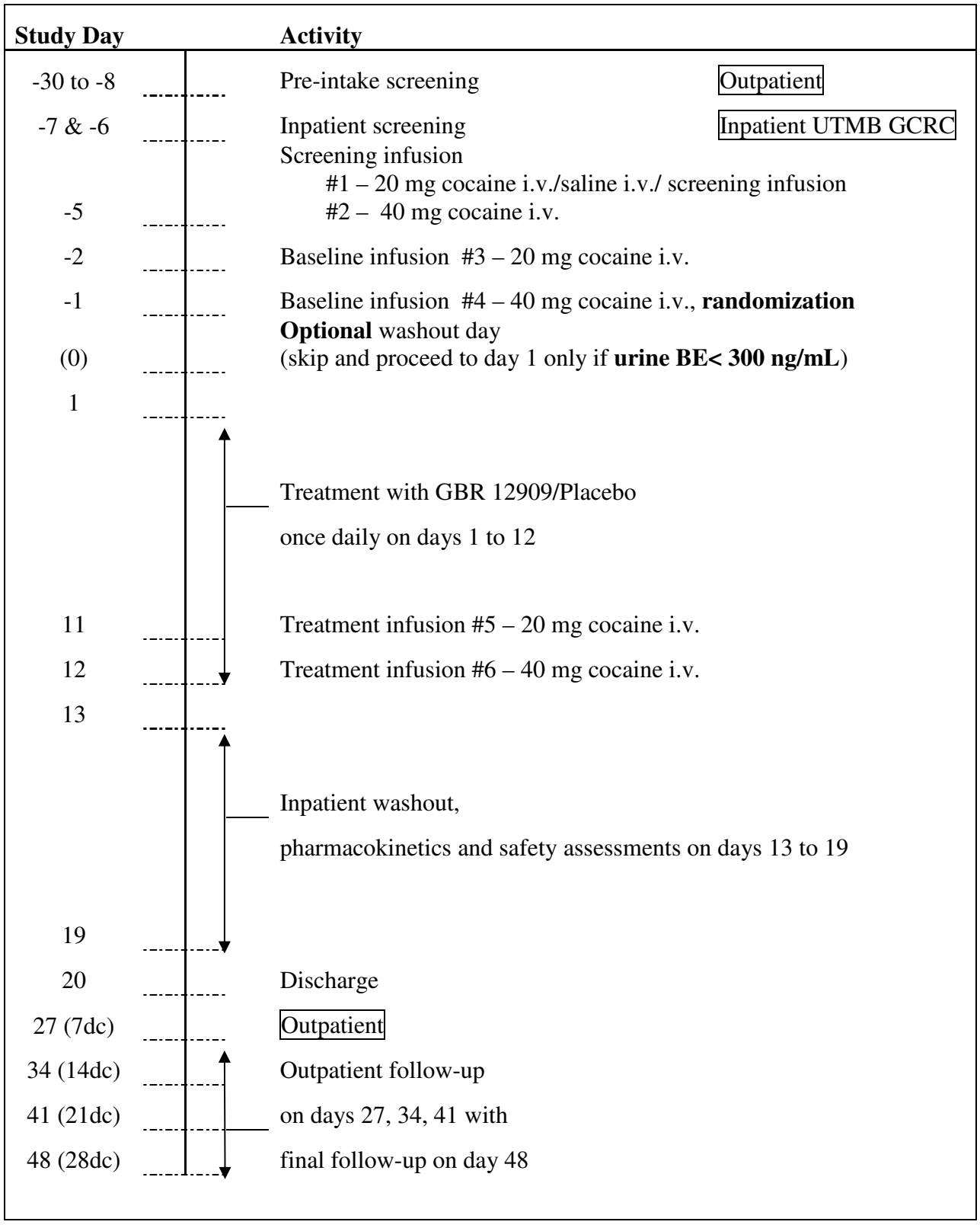
1 LIST OF ABBREVIATIONS

Abbreviation	Definition
ADME	adsorption, distribution, metabolism, and excretion
AE	adverse event
AHA	American Heart Association
ALT/SGPT	alanine aminotransferase/serum glutamic pyruvic transaminase
ARCI	Addiction Research Center Inventory
AST/SGOT	aspartate aminotransferase/serum glutamic oxaloacetic transaminase
AUC	area under the blood concentration-time curve
BE	benzoylecgonine
BDI	Beck Depression Inventory
BIS	Barratt Impulsiveness Scale
BP	blood pressure
BPRS	Brief Psychiatric Rating Scale
BSCS	Brief Substance Craving Scale
BSI	Brief Symptom Inventory
CAP	College of American Pathologists
CLIA	Clinical Laboratory Improvement Amendment of 1988
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
CPT	Continuous Performance Test
CPU	Clinical Pharmacology Unit
CRF	Case Report Form
CYP3A	cytochrome P450 isoform 3A
DA	dopamine
DAT	dopamine transporter
DMT	Delayed Memory Task
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders Fourth Edition
DSMB	Data and Safety Monitoring Board
DTR&D	Division of Treatment Research and Development
ECG	electrocardiogram
FDA	Food and Drug Administration
HR	heart rate
HRBS	HIV Risk-Taking Behavior Scale
IMT	Immediate Memory Task
IRB	Institutional Review Board
i.v.	intravenous(ly)
NIDA	National Institute on Drug Abuse

Abbreviation	Definition
PET	positron emission tomography
PK	pharmacokinetic
POMS	Profile of Mood States
PPD	purified protein derivative (tuberculin test)
RDA	recommended daily allowance
RPR	rapid plasma reagin (test for syphilis)
SAE	serious adverse event
SARC	Substance Abuse Research Center
SCID	structured clinical interview for DSM-IV
SERT	serotonin transporter
TRC	Treatment Research Clinic (part of SARC)
UCSF	University of California San Francisco
UCRC	University Clinical Research Center
UTHSC-H	University of Texas Health Science Center-Houston
UTMB	University of Texas Medical Branch- Galveston
USUHS	Uniformed Services University of the Health Sciences
VAS	Visual Analog Scale

2 STUDY SCHEMA



3 ABSTRACT

STUDY OBJECTIVES: This is a human laboratory clinical pharmacology study that will assess potential interactions between intravenous (i.v.) cocaine and three escalating oral doses (50, 70 and 100 mg) of GBR 12909, which is 1-[2-[bis(4-fluorophenyl)methoxy]ethyl]-4-(3-phenylpropyl) piperazine dihydrochloride.

Primary: The primary objective of this study is to determine safety of GBR 12909 administration and if there are significant interactions between GBR 12909 treatment concurrent with i.v. cocaine infusions of 20 and 40 mg by measuring adverse events and cardiovascular responses [heart rate (HR), blood pressure (BP), and electrocardiogram (ECG)]. Note: A significant interaction is defined as: more than 50% of the subjects treated with GBR 12909 experience a pharmacodynamic interaction when challenged with cocaine, which brings the stopping criteria (section 12.4.5) into effect.

Secondary:

1. To evaluate whether administration of GBR 12909 alters the pharmacokinetics (PK) of cocaine or its major metabolite, benzoylecgonine (BE).
2. To determine PK of GBR 12909 during treatment at 50, 75 and 100 mg doses.
3. To evaluate whether treatment with GBR 12909 alters the subjective effects of cocaine measured by Visual Analog Scale (VAS) and craving measured by Brief Substance Craving Scale (BSCS).
4. To assess the effects of GBR 12909 on mood and personality using Brief Symptom Inventory (BSI), Beck Depression Inventory (BDI), Brief Psychiatric Rating Scale (BPRS), Profile of Mood States (POMS) and HIV Risk-Taking Behavior Scale (HRBS) assessments and on the abuse liability using the Addiction Research Center Inventory (ARCI).
5. To specifically assess the effects of GBR 12909 and cocaine, separately and in combination, on impulsivity using Barratt Impulsiveness Scale (BIS) and to further explore this issue in relation to performance and specific memory measures, such as Immediate Memory Task/Delayed Memory Task (IMT/DMT).

STUDY DESIGN: This is a single dose with escalation, double-blind, placebo-controlled inpatient study, in which 24 cocaine experienced volunteers will serve as subjects. After establishing the eligibility, including cardiovascular responses to screening cocaine infusions of 20 mg and 40 mg i.v. (day -5), subjects will receive baseline cocaine infusions of 20 mg and 40 mg i.v. on two consecutive days (days -2 and -1). Up to two days between the screening infusions and the first baseline infusion (days -4 and -3) are allotted for the subjects' urine to become negative for cocaine. A full two days may not be needed for the urine to become negative. Baseline infusion #3 will take place when the urine is negative for cocaine. This will be day -2 whether or not two days have elapsed since day -5. At the end of day –1 after having completed the 2nd baseline infusion, the subjects will be randomized into three dose groups (n=8 each); in each group 6 subjects will be randomized to receive a single daily dosage of 50, 75 or 100 mg of GBR 12909 and 2 will receive matched placebo for 12 days (days 1 to 12). Following 2nd baseline infusion (day -1) and prior to initiating GBR 12909 dosing (day 1) the urine BE must be below 300 ng/mL. Note: Each cohort of 8 subjects will complete all inpatient

study procedures and be released from the clinic before starting the next cohort. Prior to initiating dosing of the next cohort, the safety data of the completed cohort including the ECG parameters (not limited to prolongation of the QT interval) will be reviewed by the NIDA medical monitor, study-independent physician and a physician representative of the governing Institutional Review Board (IRB) for a determination to proceed to dosing of the next cohort. Dosing will start at the lowest dose of GBR 12909 (50 mg) and escalate to the next higher doses sequentially (75 then 100 mg).

After beginning of daily treatment with either GBR 12909 or placebo, subjects will receive treatment cocaine infusions of 20 mg and 40 mg i.v. on two consecutive days (days 11 and 12). The subjects will be discharged 7 days after the last infusion of cocaine (day 20). Subjects will be requested to return for weekly follow-up visits for 1 month after the day of discharge (days 27, 34, 41 and 48).

STUDY DURATION: Subjects will have up to 24 days for outpatient screening at UTMB's GCRC in Galveston. A washout period will precede admission with contingent payments based on providing BE-negative urine before intake; this will preclude non-productive inpatient days. The inpatient period at UTMB's GCRC in Galveston will include two days of inpatient screening (days -7 and -6), one day of screening cocaine infusions (day -5), up to two days between screening and baseline infusions (days –4 and -3), two days of baseline cocaine infusions (days -2 and –1 including randomization), 12 days of treatment with GBR 12909 or placebo (days 1 to 12) and seven days of inpatient washout, PK sampling, safety assessments and follow-up (days 13 to 19) or until the vital signs return to baseline values. Clinic discharge is on day 20. Subjects will be requested to return weekly for 1 month for safety assessments at the GCRC.
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SAMPLE SIZE: 24 subjects total (three groups of eight). Subjects dropping out due to medical reasons not related to drug toxicity may be replaced at the discretion of the investigational team.

POPULATION: The study population will include male and female healthy, volunteer experienced cocaine users with a diagnosis of cocaine abuse or dependence according to Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) criteria and are 18-to-45 years of age.

TREATMENTS: Subjects will receive 50, 75 or 100 mg of GBR 12909 or matched placebo by oral administration once daily for 12 days. No subject will start a higher dose level until all 8 subjects (6 receiving 50 mg GBR 12909 and 2 receiving matched placebo) have completed all inpatient procedures.

ASSESSMENTS: The primary outcome measure is safety. Safety of cocaine administration in GBR 12909 dosed subjects will be measured by recording adverse events, BP, and HR, and by performing ECG monitoring. Secondary outcome measures include pharmacokinetic parameters and psychological assessments. Pharmacokinetic interactions between cocaine and GBR 12909 will be assessed by collecting blood and determining levels of cocaine and BE and peak and trough levels of GBR 12909 during cocaine treatment infusions (sessions #5 and 6). The effect of GBR 12909 on cocaine craving will be assessed by BSCS; other psychological assessments include POMS, BSI, BDI, VAS, ARCI, BPRS, HRBS, BIS and IMT/DMT.

4 INTRODUCTION AND RATIONALE

4.1 Therapeutic Strategies for Treating Cocaine Abuse

Cocaine abuse and dependency in the United States have achieved epidemic proportions in the past decade and constitute a significant public health concern. The development of a pharmacological treatment for cocaine abuse and dependence is a major objective of the National Institutes on Drug Abuse (NIDA) that is being coordinated by Division of Treatment Research and Development (DTRD). A variety of neuropharmacological strategies are being pursued in the search for an effective treatment for cocaine abuse. These include: 1) blocking cocaine's effects, 2) restoration of central nervous system homeostasis, 3) reducing craving or enhancing the addict's ability to manage his/her response to craving, 4) treating underlying comorbid conditions that may predispose targeted subpopulations toward dependence, and 5) stress reduction to prevent relapse.

4.1.1 Use of Dopaminergic and Serotonergic Agents to Treat Cocaine Dependency

In the mid-90s, after the earlier pharmacologic trials of tricyclic antidepressants to treat cocaine dependence (Gawin, 1986; Giannini *et al.,* 1986), the search for an effective pharmacotherapy for cocaine addiction was focused on dopaminergic agents (bromocriptine, bupropion, cabergoline) with direct or indirect agonist activity at dopamine receptors (Johanson and Schuster, 1995). This approach is based on a combination of theory and experimental data indicating that a) cocaine binds at the dopamine transporter and inhibits neurotransmitter reuptake, thus leading to a build-up of extracellular dopamine levels and potentiation of DAergic neurotransmission in mesolimbocortical pathways (Kuhar *et al*., 1991), and b) chronic cocaine use depletes brain dopamine, which is experienced as increased cocaine craving. Thus, influence on drug seeking behavior via restoration of dopamine levels may be achieved by treatment with a) dopamine agonists, b) inhibitors of MAO that convert dopamine into dihydroxyphenylacetic acid, and c) inhibitors of catechol-*O*-methyltransferase that converts dihydroxyphenylacetic acid into homovanillic acid.

The results of recent studies indicating that serotonin and norepinephrine receptors are also involved in cocaine addiction (Sora *et al.,* 2001), fostered concepts that utilize the structure of dopamine transporter (DAT) domains involved in cocaine recognition (Kitayama *et al.,* 1993; Lin *et al.,* 1999) and the sequence homologies between DAT and serotonin transporter (SERT) (Uhl and Hartig, 1992) for a rational design of new drugs to treat cocaine dependence.

The present study will investigate GBR 12909, a dopamine reuptake inhibitor, as a potential cocaine dependency medication.

4.1.2 GBR 12909 as a Potential Cocaine Dependency Medication

Cocaine is a stimulant as well as a local anaesthetic with potent vasoconstrictor properties (i.e., cocaine rapidly increases HR and BP in a dose related manner). It induces a complex pattern of subjective effects that have been described as intense euphoria and alertness, mood enhancement, increased confidence and strength, heightened sexual feelings and indifference to concerns or cares. The neurobiological mechanism underlying the effects of cocaine are not well understood. There is considerable evidence that the initiation and continuation of cocaine use is associated with the effects of the drug on the dopaminergic, serotonergic and noradrenergic modulation of

the central nervous system function. Animal studies suggest that the mesocorticolimbic dopaminergic pathways are important mediators of cocaine's reinforcing properties.

Although many compounds have been evaluated for the treatment of cocaine dependence, so far there is no pharmacotherapy for this indication. Cocaine is known to produce its major abuse-related effects via dopaminergic mechanisms in the midbrain. It binds at the dopamine transporter (DAT) and inhibits dopamine (DA) reuptake, thus leading to a build-up of extracellular DA levels and stimulation of reward-associated mesolimbocortical pathways (Kuhar *et al.,* 1991). Cocaine is a potent inhibitor of not only DAT; it also inhibits transporters for serotonin and norepinephrine (Fleckenstein *et al.,* 2000; Miller *et al.,* 2001). Single gene knockout studies of dopamine, serotonin or norepinephrine transporters in mice indicate that any one of these transporters might be able to mediate cocaine reward in the other's absence (Sora *et al.,* 1998; Xu *et al.,* 2000). Sora *et al.* (2001) found that cocaine reward depends on both DAT and SERT blockade and that serotonin, as well as dopamine, plays a critical role in the development of cocaine addiction. Still, the effects of transporter gene copy numbers on the cocaine place preference test indicate a greater role for DAT than serotonin transporter (SERT) in cocaine reward/reinforcement in mice, consistent with previous pharmacological studies.

Given the obvious importance of DAT in the addictive properties of cocaine, the development of compounds that target DAT represents a logical approach for treatment of cocaine dependence. *In vitro* preclinical studies have shown that GBR12909 has a strong affinity for the dopamine transporter. GBR12909 produces dopamine like agonist effects in preclinical studies and the finding that GBR12909 has a long duration suggests it may be a potential agonist medication (Rothman and Glowa, 1995). Furthermore, nonhuman primate studies have demonstrated that GBR12909 can selectively block cocaine self-administration (Villemagne *et al.,* 1999a). Limited reinforcing properties of GBR 12909 may be advantageous in the context of addiction treatment programs by contributing to better patient's compliance and enhanced effectiveness of medication (Howell and Wilcox, 2001).

The present study, which will examine the safety of the investigational compound, GBR12909, and the potential interaction between GBR 12909 and cocaine in cocaine-experienced volunteers, is necessary prior to subsequent randomized trials designed to assess therapeutic efficacy for the treatment of cocaine abuse and dependence.

4.2 GBR 12909

4.2.1 Pharmacology

GBR 12909, 1-[2-[bis(4-fluorophenyl)methoxy]ethyl]-4-(3-phenylpropyl) piperazine dihydrochloride], is a DA uptake inhibitor structurally different from cocaine. GBR 12909 binds to the DA transporter (DAT) and inhibits reuptake of DA from the synaptic cleft. GBR 12909 exhibits high affinity to DAT (K*i* for human DAT is 9 nM), which is 20-fold higher than that of cocaine (NIDA, unpublished data). *In vivo* and *in vitro* pharmacological and biochemical studies have demonstrated that GBR 12909 is a selective DA uptake inhibitor with specificity for DA uptake 100-fold higher compared to noradrenaline and serotonin uptake (Andersen, 1989; Sogaard *et al.,* 1990). GBR 12909 is a long-acting inhibitor of DA uptake, and duration of its effect on DAT availability and increase in DA in conscious monkey brain is 5.5 and 7 hrs,

respectively, as evaluated by positron emission tomography (PET) studies combined with microdialysis (Tsukada *et al.,* 2000).

GBR 12909 produces a persistent and non-competitive blockade of DAT and substantially reduces cocaine-induced increases in extracellular DA in the nucleus accumbens of the rats (Rothman *et al.,* 1991; Baumann *et al.,* 1994). *In vivo* microdialysis studies in rodents showed that GBR 12909 attenuates cocaine and amphetamine-induced increases in mesolimbic DA that mediate the addictive and reinforcing properties of drugs of abuse (Rothman *et al.,* 1991; Baumann *et al.,* 1994).

Early data showed that GBR 12909 can decrease cocaine-maintained response in *Rhesus* monkeys without affecting similar levels of food-maintained response (Glowa *et al.,* 1995a,b). Furthermore, a decanoate ester of a hydroxylated analog of GBR 12909, DBL-583, can decrease cocaine-maintained response by 80% without affecting food-maintained response; this effect lasts almost 30 days with a single injection (Glowa *et al.,* 1996). Intravenous (i.v.) infusion of GBR 12909 (1 mg/Kg) to *Papio anubis* baboons inhibits amphetamine-induced striatal DA release by 74% as measured by raclopride PET scans (Villemagne *et al.,* 1999b). Importantly, GBR 12909 reduces (1 mg/Kg, i.v.) and eliminates (3 mg/Kg, i.v.) cocaine self-administration in *Rhesus* monkeys (Villemagne *et al.,* 1999a). The doses of GBR 12909 that suppress cocaine self-administration in non-human primates produce high occupancy of DAT; thus, doses of 1, 3 and 10 mg/Kg occupy 26, 53, and 72% of DAT, respectively (measured by WIN35,428 PET scans) (Villemagne *et al.,* 1999a). GBR 12909 produces a dose-dependent DAT occupancy in humans as well, and at 100 mg oral doses, the DAT occupancy by GBR 12909, as assessed by PET imaging with WIN35,428, is reported to be 30 to 40 % (Wong *et al.,* 1999). The results of the studies in non-human primates and in human volunteers indicate that GBR suppresses cocaine self-administration via inhibition of DAT and that human laboratory studies testing the efficacy of orally administered GBR 12909 for cocaine addiction should use doses that produce sufficiently high occupancy of DAT (Glowa and Rothman, 1995).

4.2.2 Pharmacokinetics

The results of GBR 12909 pharmacokinetics studies in humans indicate that:

1. GBR 12909 metabolism follows first order kinetics with elimination half-life of about 48 hours (Sogaard *et al.,* 1990).
2. Steady-state concentrations of GBR 12909 are reached by day 8 of repetitive dosing (Sogaard *et al.,* 1990; NIDA Communication, 2001).
3. Food intake increases oral bioavailability of GBR 12909 (Ingwersen *et al.,* 1993b).
4. GBR 12909 is rapidly absorbed with a mean T_{max} of less than 1.5 hours (NIDA Communication, 2001).

4.2.3 Metabolism

GBR 12909 is metabolized by human liver microsomes and by human hepatocytes to a single metabolite, the chemical structure and biological activity of which remains to be elucidated (Cherstniakova *et al.,* 2001). A recent study of GBR 12909 biotransformation by human liver microsomes (Cherstniakova *et al.,* 2001) indicated that CYP3A, a ketoconazole-inhibited member of the cytochrome P450 family of drug-metabolizing monooxygenases, appears to be

the major enzyme responsible for GBR 12909 degradation. The results of this study indicate that coadministration of GBR 12909 with specific inhibitors or inducers of CYP3A such as ketoconazole, ritonavir and rifampin could alter expected therapeutic effects in cocaine-dependent subjects.

Although cocaine is primarily metabolized by esterases in the plasma and liver to inactive metabolites, benzoylecgonine (BE), ecgonine methyl ester, and ecgonine (Stewart *et al.,* 1977; Kloss *et al.,* 1984; Dean *et al.,* 1991), a very small portion of cocaine is oxidized to an active metabolite norcocaine by hepatic microsomal enzyme CYP3A (Ladona *et al.,* 2000). The fact that both GBR 12909 and cocaine are substrates for CYP3A indicates a potential of cocaine-GBR 12909 interaction that may lead to a possible inhibition of each substrate's metabolism by CYP3A. However, norcocaine is a minor metabolite that accounts for only 2 to 6% of the administered cocaine dose (Inaba *et al.,* 1978), and thus the effect of GBR 12909 on cocaine metabolism should be negligible.

4.2.4 Previous Human Experience with GBR 12909

Two randomized placebo-controlled double-blind cross-over studies in normal human volunteers (20-45 years old) have been conducted by Sogaard *et al.* (1990) with rising dose levels of GBR 12909 in an aqueous solution. The first single dose study was conducted in four subjects with dose levels of 100, 200 and 300 mg with a 7 day washout period between each dose level. Subjects fasted from 8 hours before and 2 hours after the dosing. C_{max} ranged from 29-102 nM after the 100 mg dose, from 119-348 nM after the 200 mg dose and from 266-831 nM after the 300 mg dose. GBR 12909 was rapidly absorbed with T_{max} ranging from 0.5-1 hr. The elimination half-life was not characterized due to lack of assay sensitivity.

A multiple dose study has been performed with dose levels of 50, 100 and 150 mg administered for 7 days in four subjects (Sogaard *et al.,* 1990). Subjects fasted from 8 hours before and 30 minutes after the dosing. Serum concentrations observed 24 hours after the last dose ranged from 33-70 nM after the 100 mg dose and 83-153 after the 150 mg dose. Concentrations after the 50 mg dose were below the detection limit (20 nM). The terminal half-life was not calculated in this study. However, rough estimates indicated a value between 36-57 hours. Subjects, in that study, demonstrated mild to moderate side effects such as difficulties in concentration, asthenia, feeling of drug influence and palpitations. In addition, a dose related effect on ECG T-wave amplitude was mentioned in the report. One of 4 subjects demonstrated an abnormal prolongation in the QT-interval at the highest doses. No signs of arrhythmia or cardiac decompensation during exercise until exhaustion were observed. In addition, dose related sedation was observed in the single dose study assessed by psychomotor performance. The report also noted that there were no changes in hematologic and blood chemistry parameters. Finally, the study noted that pharmacokinetics observed in individuals appeared to be first order in nature with elimination half-life estimated at one to two days. The authors concluded that steady state serum concentrations of GBR 12909 appeared to be obtained within one week of once daily dosing and that the expected "therapeutic" doses of the agent appeared to be well tolerated in the subjects.

In a three-way cross-over study in 14 healthy volunteers, GBR 12909 exhibited nonlinear pharmacokinetics after multiple administrations of daily doses of 25, 75 and 125 mg for 14 days.

Near-steady state concentrations were achieved in 9-11 days. The mean elimination half-life was approximately 60 hours at 75 and 125 mg doses (Ingwersen *et al,* 1993a).

An increase in oral bioavailability following administration of a single dose of 100 mg of GBR 12909 with food was observed in a study conducted in 12 healthy male volunteers. The AUC_{0-t} increased from 110 to 194 nM.h after a low fat diet and from 110 to 391 nM.h after a high fat diet (Ingwersen *et al,* 1993b).

A recent NIDA-sponsored phase 1, dose escalation protocol was completed at the NIDA-Uniformed Services University of the Health Sciences (USUHS) Clinical Pharmacology Unit (CPU). This study examined 12 healthy male and female volunteers, ages 18-to-45 years old, in a dose escalation scheme incorporating 25, 50, 75, and 100 mg daily dosages of GBR 12909 (NIDA Communication, 2001). The primary finding of this study was a slight increase in heart rate and systolic blood pressure in the majority of subjects at the higher doses (75 mg and 100 mg); this slight increase in HR and BP did not completely revert to baseline between successive dose levels. ECG effects of GBR 12909 were not significant at the dosages examined; a slight, clinically insignificant increase in the QTc interval was seen, which was attributed entirely to the increase in HR. Two of the 12 subjects completing the protocol experienced an increased sexual drive at the two higher dosages of GBR 12909. No significant safety issues appeared from the psychometric data at any of the 4 tested doses of GBR 12909 (25, 50, 75 or 100 mg). There were no serious adverse events or dose-limiting toxicity.

4.2.5 Rationale for the Current Study

Before clinical investigations to determine GBR 12909 efficacy as a pharmacological treatment for cocaine abuse and dependence can proceed, a thorough study of the safety, tolerability and pharmacokinetics of the agent is required. GBR12909 has been investigated previously in European clinical studies for the treatment of depression and Parkinson's disease and for safety in healthy human volunteers but these studies utilized only small numbers of subjects in both single dose and multiple dose schedules (Sogaard *et al.,* 1990; Ingwersen *et al,* 1993a,b). A recent NIDA-USUHS CPU study of GBR 12909 was not placebo-controlled and was conducted in healthy volunteers (NIDA Communication, 2001). A more thorough study of potential hemodynamic effects of GBR 12909 in the indicated population (cocaine users) is required for further development of this compound as a potential therapy to treat cocaine dependency. An ongoing phase 1 absorption, distribution, metabolism, and excretion (ADME) clinical trial of GBR 12909 is conducted in cocaine experienced healthy volunteers to further examine the safety of GBR 12909.

The present study constitutes the next step in phase 1 investigations, which is to examine the potential interaction between GBR 12909 and cocaine in cocaine experienced volunteers to demonstrate that GBR 12909 can be used safely in a population likely to use cocaine concurrently with GBR 12909 and to explore whether and how GBR 12909 might affect cocaine pharmacokinetics. Planned dosage levels for the present phase 1 clinical study encompass the expected "therapeutic" dose of 50-100 mg of GBR 12909 per day. Furthermore, the three dose levels planned for this study (50, 75 and 100 mg) are well within the range, which has previously been used in human subjects in Europe.

4.2.6 Safety of GBR 12909

The pharmacokinetics of GBR 12909 may be affected by drugs that alter (induce or inhibit) CYP3A activity that is responsible for biotransformation of GBR 12909 (Cherstniakova *et al.,* 2001). Thus, coadministration of GBR 12909 with specific inhibitors/inducers of CYP3A such as ketoconazole, ritonavir and rifampin should be done with caution because that can alter expected therapeutic effects of GBR 12909 in cocaine-dependent subjects. These agents can either reduce GBR 12909 metabolism and increase its plasma concentrations leading to toxicity or increase clearance of GBR 12909, resulting in lower plasma levels of this drug and, perhaps, sub-effective dosing. Also, as GBR 12909 potently inhibits human recombinant CYP2D6 *in vitro* (K_i 0.13 nM) (NovaScreen Biosciences,1991), it may have the potential to decrease the metabolism and consequently increase the toxicity of drugs known to be metabolized by CYP2D6 such as clozapine, codeine, risperidone, haloperidol, dextromethorphan, and fenfluramine. Thus, close monitoring of plasma GBR 12909 concentration and its adverse effects will be performed.

Adverse events reported in subjects receiving GBR 12909 include mild to moderate difficulties in concentration, asthenia, feelings of drug influence and palpitations. In addition, a dose related effect on ECG T-wave amplitude was mentioned in one report. In one study, 1 of 4 subjects, demonstrated a slightly abnormal prolongation in the QT-interval at a 150 mg daily dose. In studies conducted by NIDA with 25 to 100 mg daily dosages of GBR 12909, a slight increase in heart rate and systolic blood pressure was reported in the majority of subjects (NIDA Communication, 2001).

4.3 Cocaine

4.3.1 Pharmacology.

Cocaine is a potent inhibitor of monoamine transporters including dopamine, serotonin, and norepinephrine transporters (Fleckenstein *et al.,* 2000; Miller *et al.,* 2001). Cocaine binds at the dopamine transporter and inhibits neurotransmitter reuptake, leading to a build-up of extracellular dopamine levels and potentiation of mesolimbocortical pathways (Kuhar et al., 1991). Neuroimaging (positron emission tomography) studies of human volunteers who regularly abuse cocaine indicate that doses used by cocaine abusers lead to a significant brain dopamine transporter blockade, which is associated with subjective effects of cocaine (self-reported "high") (Volkow *et al.,* 1997). Single gene knockout studies in mice of dopamine, serotonin or norepinephrine transporters indicated that any one of these transporters might be able to mediate cocaine reward in the other's absence (Sora *et al.,* 1998; Xu *et al.,* 2000). Sora et al. (2001) found that cocaine reward depends on both DAT and SERT blockade and that serotonin, as well as dopamine, plays a critical role in the development of cocaine abuse/dependence. The effects of transporter gene copy numbers on the cocaine place preference test indicated a greater role for DAT than SERT in cocaine reward/reinforcement in mice, consistent with previous pharmacological studies. Thus, mice with even a single DAT gene copy and no SERT copies still experienced reward/reinforcement behavior following cocaine administration, while cocaine-induced reward/reinforcement behavior was totally blocked in mice with no DAT gene and either half-normal or absent SERT.

Cocaine affects nearly every organ and system, with the most dramatic changes being observed in the cardiovascular system and the brain. An important factor of cocaine-induced toxicity is vasoconstriction of coronary arteries and cerebral blood vessels combined with increased platelet aggregation, which can lead to focal or general ischemic episodes and myocardial and cerebral infarctions. In the cardiovascular system, tachycardia, hypertension, ruptures of blood vessels, arrhythmias, and arteriosclerotic lesions are typical complications of cocaine abuse that often precede myocardial ischemia and infarction (Karch, 1993). Chronic use of cocaine can result in serious neuropathies, including optic nerve neuropathy, and can lead to seizures, cerebral infarction, cerebral hemorrhage, multifocal cerebral ischemia, and cerebral atrophy (Majeska *et al.,*1996). Psychiatric impairments associated with cocaine abuse include cognitive deficits, particularly in attention, problem solving, abstraction, arithmetic performance and short-term memory (Majeska *et al.,*1996). The most significant psychopathologies observed in cocaine addicts include anhedonia, anxiety, anergy, paranoia, depression, and bipolar mood disorder, which may predispose to suicide and are believed to contribute to cocaine craving and relapse. Cocaine seems to be hepatotoxic in humans (Marks and Chapple, 1967; Kloss *et al.,* 1984); this hepatotoxicity is enhanced by drugs such as barbiturates, alcohol and cocaine adulterants. Cocaine also induces pulmonary disorders, which are particularly severe in cocaine smokers. These disorders include barotrauma, inflammation and lung infections, pulmonary congestion, edema, hypertrophy of pulmonary arteries, and pulmonary necrosis (Karch, 1993).

4.3.2 Cocaine Pharmacokinetics.

The distribution half-life of cocaine from an intravenous (i.v.) dose is about 10 min and the elimination half-life of cocaine is about 1 hour (50-80 min) (Jeffcoat *et al.,* 1989).

4.3.3 Cocaine Metabolism.

Cocaine is primarily metabolized by esterases in the plasma and liver to inactive metabolites, benzoylecgonine (BE), ecgonine methyl ester and ecgonine (Stewart *et al.,* 1977; Kloss *et al.,* 1984; Dean *et al.,* 1991). A very small portion of cocaine is metabolized by hepatic microsomal enzyme CYP3A to an active metabolite, norcocaine (N-demethyl metabolite) (Ladona *et al.,* 2000); however norcocaine is a minor metabolite that accounts for only 2 to 6% of the administered cocaine dose (Inaba *et al.,* 1978). In the presence of ethanol, liver carboxylesterase catalyzes the ethyl transesterification of cocaine to form cocaethylene plus methanol (Dean *et al.,* 1991).

4.3.4 Cocaine Dose Justification.

Intravenous cocaine administration spanning the doses proposed for use in this study (20 mg and 40 mg) have been previously investigated in human laboratory clinical trials (Johnson *et al.,* 1998; Walsh *et al.,* 1994). Johnson and colleagues conducted continuous non-invasive cardiovascular monitoring in eight healthy cocaine addicts receiving intravenous doses of cocaine 0.325 mg/kg or 0.650 mg/kg. They demonstrated dose dependent increases in pulse and mean arterial pressure following cocaine administration that peaked 5 min post-cocaine infusion with a maximal responses being sustained for a further 15 and 35 min afterwards, respectively. Cocaine administration had no significant effect on peripheral oxygen saturation, and no clinical abnormalities of rhythm or conductivity were seen on ECG. These doses of cocaine (20 mg and 40 mg) and the method of single-dose i.v. cocaine administration as well as procedures for cardiovascular monitoring appear to be relatively safe for laboratory studies of healthy cocaine

addicts with no pre-existing cardiovascular disease. Importantly, in a phase 1 clinical trial study of fluoxetine, intravenous cocaine doses of 20 mg and 40 mg did not produce any adverse physiological or subjective reactions in 5 healthy adult male volunteers with histories of cocaine abuse (Walsh *et al.,* 1994).

5 STUDY DESIGN

This is a single dose with escalation, double-blind, placebo-controlled inpatient study, in which 24 cocaine experienced volunteers will serve as subjects. After establishing the eligibility, including cardiovascular responses to screening cocaine infusions of 20 mg and 40 mg i.v. (day -5), subjects will receive baseline cocaine infusions of 20 mg and 40 mg i.v. on two consecutive days (days -2 and -1). Up to two days between the screening infusions and the first baseline infusion (days -4 and -3) are allotted for the subjects' urine to become negative for cocaine. At the end of day –1 after having completed the 2nd baseline infusion, the subjects will be randomized into three dose groups (n=8 each); in each group 6 subjects will be randomized to receive a single daily dosage of 50, 75 or 100 mg of GBR 12909 and 2 will receive matched placebo for 12 days (days 1 to 12). Following 2nd baseline infusion (day -1) and prior to initiating GBR 12909 dosing (day 1) the urine BE must be below 300 ng/mL. Note: Each cohort of 8 subjects will complete all inpatient study procedures and be released from the clinic before starting the next cohort. Prior to initiating dosing of the next cohort, the safety data of the completed cohort including the ECG parameters (not limited to prolongation of the QT interval) will be reviewed by the NIDA medical monitor, study-independent physician and a physician representative of the governing Institutional Review Board (IRB) for a determination to proceed to dosing of the next cohort. Dosing will start at the lowest dose of GBR 12909 (50 mg) and escalate to the next higher doses sequentially (75 then 100 mg).

After beginning of daily treatment with either GBR 12909 or placebo, subjects will receive treatment cocaine infusions of 20 mg and 40 mg i.v. on two consecutive days (days 11 and 12). The subjects will be discharged 7 days after the last infusion of cocaine (day 20). Subjects will be requested to return for weekly follow-up visits for 1 month after the day of discharge (days 27, 34, 41 and 48).

Plasma concentrations for GBR 12909 will be measured at specified time-points during the inpatient period and during the 120 hours following the dose on the 12th day of inpatient period. Safety will be assessed by physical examinations, vital signs, 12-lead ECGs, routine hematology, routine serum chemistry, urinalyses, and monitoring for adverse experiences. Subjects will be monitored for central nervous system (CNS) effects using psychometric determinations during the inpatient period and during the outpatient follow-up visits.

6 STUDY OBJECTIVES

Primary: The primary objective of this study is to determine safety of GBR 12909 administration and if there are significant interactions between GBR 12909 treatment concurrent with i.v. cocaine infusions of 20 and 40 mg by measuring adverse events and cardiovascular responses [heart rate (HR), blood pressure (BP), and electrocardiogram (ECG)]. Note: A significant interaction is defined as: more than 50% of the subjects treated with GBR 12909

experience a pharmacodynamic interaction when challenged with cocaine, which brings the stopping criteria (section 12.4.5) into effect.

Secondary:

1. To evaluate whether administration of GBR 12909 alters the pharmacokinetics (PK) of cocaine or its major metabolite, benzoylecgonine (BE).
2. To determine PK of GBR 12909 during treatment at 50, 75 and 100 mg doses.
3. To evaluate whether treatment with GBR 12909 alters the subjective effects of cocaine measured by Visual Analog Scale (VAS) and craving measured by Brief Substance Craving Scale (BSCS).
4. To assess the effects of GBR 12909 on mood and personality using Brief Symptom Inventory (BSI), Beck Depression Inventory (BDI), Brief Psychiatric Rating Scale (BPRS), Profile of Mood States (POMS) and HIV Risk-Taking Behavior Scale (HRBS) assessments and on the abuse liability using the Addiction Research Center Inventory (ARCI).
5. To specifically assess the effects of GBR 12909 and cocaine, separately and in combination, on impulsivity using Barratt Impulsiveness Scale (BIS) and to further explore this issue in relation to performance and specific memory measures, such as Immediate Memory Task/Delayed Memory Task (IMT/DMT).

7 STUDY SITE

The study will be conducted at one site, which is UTMB's General Clinical Research Center in Galveston. The study was originally developed by and a grant was obtained from NIDA by Dr. Grabowski at UTHSC-H. Because it was not possible to do the study at UTHSC-H, Dr. Cunningham agreed to be the PI for the study at UTMB and to assemble an investigative team that includes the physicians needed to conduct the study on the GCRC, and Dr. Grabowski agreed to provide support to UTMB from his NIDA grant.

8 STUDY SPONSOR

This study will be conducted under IND No. 57,007 held by NIDA.

9 SUBJECT SELECTION

9.1 Inclusion Criteria

In order to participate in this study, subjects must:

1. Be between 18 and 45 years-of-age inclusive.
2. Be within 20% of ideal body weight and must weigh at least 45 kg. (MetLifeInsTable)
3. Understand the study procedures and provide written informed consent.

4. Be volunteers who are dependent on or abusing cocaine according to DSM-IV criteria and are non-treatment seeking at time of study.
5. Currently use cocaine as determined by self report and a positive urine test for BE within 30 days of the start of the study.
6. Be male, or if female, have a negative pregnancy test within 72 hours prior to receiving the first dose of investigational agent and agree to use one of the following methods of birth control, or be postmenopausal, or have had hysterectomy or have been sterilized.
    a. complete abstinence from sexual intercourse
    b. diaphragm and condom by partner
    c. intrauterine device and condom by partner
    d. sponge and condom by partner
7. Note: oral contraceptives, Depo-Provera, Norplant and intrauterine progesterone contraceptive system are not allowed.
8. Be judged by the examining physician or his/her designee after a history and physical examination to be in good health, without clinically significant abnormalities.
9. Have an ECG performed that demonstrates normal sinus rhythm and no clinically significant abnormalities.

NOTE: Recent intermittent alcohol or other illicit drug use without physical dependence is allowable.

9.2 Exclusion Criteria

In order to participate in the study, subjects must not:

1. According to DSM-IV criteria as determined by structured clinical interview (SCID), have any current diagnosis or history of major psychiatric illness other than drug dependence or disorders secondary to drug use or be mentally or legally incapacitated.
2. According to DSM-IV criteria be dependent upon or abusing drugs other than cocaine, marijuana, nicotine, and alcohol or have physiological dependence upon alcohol requiring medical detoxification.
3. Currently be physically dependent on illicit drugs besides cocaine and marijuana as determined by the SCID. Note: The subjects that are not physically dependent on other illicit substances but during pre-study screening have a positive urine drug screen for amphetamines, barbiturates, benzodiazepines, methadone, opiates, PCP, or propoxyphene will be allowed to participate after a wash-out period and providing a negative urine drug screen.
4. Use any prescription drugs within 14 days of enrollment or non-prescription drugs within 7 days of enrollment, or if female, have used an oral contraceptive, Depo-Provera,

Norplant or intrauterine progesterone contraceptive system within 30 days of enrollment (in the case of DP or Norplant, if within the past 3 months).

5. Be pregnant or lactating.
6. Have a history of liver disease or current elevation of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) exceeding the upper limit of normal.
7. Have donated a unit of blood or participated in any other clinical investigation within 4 weeks of enrolling on the study.
8. Have a history of any illness, or a family history of early significant cardiovascular disease, or a history of behavior, that in the opinion of the investigator might confound the results of the study or pose additional risk in administering the investigational agents to the subject.
9. Be seropositive for hepatitis B surface antigen, hepatitis C antibody, or human immunodeficiency virus (HIV) types 1 and 2.
10. Be seropositive for syphilis by rapid plasma reagin (RPR) test or have active tuberculosis with positive purified protein derivative (PPD) skin test confirmed by chest x-ray.
11. Have a diagnosis of adult (i.e., 21 years or older) asthma, or chronic obstructive pulmonary disease (COPD), including those with a history of acute asthma within the past two years, and those with current or recent (past 2 years) treatment with any inhaled or oral beta-agonist.
12. Be unable to distinguish between a 20 mg and 40 mg dose of cocaine intravenously.

10 INVESTIGATIONAL AGENTS

10.1 GBR 12909 and Placebo

The chemical name of GBR 12909 is 1-(2[bis(4-fluorophenyl)methoxy[ethyl)-4-(3-phenylpropyl) piperazine dihydrochloride. GBR 12909 will be supplied as 25 mg and 50 mg gelatin capsules along with matched placebo capsules by the National Institute on Drug Abuse (NIDA). These capsules were manufactured by Murty Pharmaceuticals (Lexington, Kentucky) under a contract with NIDA. GBR 12909 is supplied as white opaque 25 mg and 50 mg capsules, weighing 300 mg. Specifications of other constituents of GBR 12909 capsules are as follows:

Ingredient	Placebo	25 mg capsule	50 mg capsule
GBR 12909	0 mg	25 mg	50 mg
Lactose Monohydrate, NF	210 mg	185 mg	168 mg
Microcrystalline Cellulose, NF	92 mg	82 mg	74 mg
Croscarmelose Sodium, NF	6 mg	6 mg	6 mg
Colloidal Silicon Dioxide, NF	1 mg	1 mg	1 mg
Magnesium Stearate, USP/NF	1 mg	1 mg	1 mg

10.2 Cocaine

Cocaine Hydrochloride solutions, 10 mg/mL in 2 mL ampoule (20 mg dose) and 20 mg/mL in 2 mL ampoule (40 mg dose) will be manufactured by Murty Pharmaceuticals for NIDA. The Cocaine Hydrochloride solutions should be stored in the pharmacy vault under refrigerated conditions. Standard controlled substance procedures will govern access to the drug. Cocaine will be administered by i.v. infusion over 60 seconds by the study physician. Any unused drug will be disposed according to standard practices.

10.3 Dispensing Investigational Agents

Investigational agents will be administered under the supervision of research staff. The 50 mg dose will be administered as a single 50 mg capsule, the 75 mg dose will be administered as one 50 mg and one 25 mg capsule and the 100 mg dose will be administered as two 50 mg capsules. This same schema will be used for the matched placebo. GBR 12909 will be ingested once every 24 hours in the fasted state (nothing by mouth except water after midnight until two hours after dose) at 7:00 a.m. Subjects will be instructed to take each dose of their study medication with approximately 250 mL of water and their oral cavity will be visually examined by the research nurse to ensure the medication has been ingested. Specific instructions for each treatment are as follows: "Take each pill with 250 mL of water, once daily in the morning."

10.4 Packaging, Labeling, Storage, and Return of Investigational Agents

Investigational agents will be packaged in high-density polyethylene bottles. Bottles will be labeled with the subject's allocation number, dose level (for placebo this will be the dose level of the cohort), treatment day, quantity/container, and instructions for taking the medication. The investigational agents should be stored at room temperature, and exposure to direct light should be avoided. The GBR 12909 is stable for 31 months-long storage at 25^{o}C and relative humidity of 60%.

Investigational clinical supplies must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated assistants have access. Clinical supplies are to be dispensed/administered as described above. At the end of the study, all unused clinical supplies must be returned to NIDA.

11 TREATMENT PLAN

11.1 GBR 12909 and Placebo

Each subject will receive twelve (12) days of GBR 12909 or matched placebo at the dose assigned to their cohort (50, 75 or 100 mg) starting on study day 1.

11.2 Cocaine

All subjects will receive cocaine infusions on five days: days -5, -2, -1, 11 and 12. Cocaine will be administered by i.v. push over 60 seconds by the study physician. On day -5 (screening infusions #1 and #2 to determine eligibility), subjects will receive 20 mg cocaine i.v. followed 2 hours later by saline infusion and then 2 hours later by 40 mg cocaine i.v. Subjects will receive

baseline cocaine infusions on two consecutive days, day -2 (session #3, 20 mg cocaine i.v.) and day -1 (session #4, 40 mg cocaine i.v.). Subjects will receive treatment cocaine infusions on day 11 (session #5, 20 mg cocaine i.v.) and on day 12 (session #6, 40 mg cocaine i.v.); these infusions will be concurrent with GBR 12909 administration and thus examine the interactions.

For each baseline and treatment session, subjects will be randomly assigned (1:1 ratio) to receive either saline (at 10:00 a.m.) followed one hour later by cocaine or cocaine (at 10:00 a.m.) followed one hour later by saline in a double-blind fashion (subjects and research staff will be blinded). During the treatment sessions #5 and #6 (study days 11 and 12), subjects will take GBR 12909 in a fasting state at 7:00 a.m., fast another 2 hours until breakfast at 9:00 a.m. and after that will get the infusions at 10:00 a.m. and 11:00 a.m.

11.3 Prior and Concomitant Medication(s)

No prescription medication for 14 days and non-prescription medications (including health food supplements) for 7 days are to be taken by subjects prior to the inpatient evaluation. Female subjects must not use oral contraceptives, Depo-Provera, Norplant and intrauterine progesterone contraceptive system 30 days prior to study participation (in the case of DP or Norplant, if within the past 3 months). Addition of any medication during the course of the study must be discussed with the NIDA medical monitor prior to administration. Should there be a clinical indication for any additional medication during the course of the study, the name of the drug, dosage, reason for administration, and duration of administration must be recorded on the appropriate case report form (CRF). One multivitamin per day that does not exceed 100% of the recommended daily allowance (RDA) for each component is permitted for ingestion by each subject except during inpatient periods.

11.4 Dietary, Activity, and Other Restrictions

Diet. For all dosages of GBR 12909, subjects must not consume any food or drink except water from midnight to 2 hours following each dose. Each dose must be taken with at least 250 mL of water. Except for these restrictions around the time of dosing, there will be no other dietary restrictions during the study except all food and drink must be provided by UTMB's GCRC.

Snacks are permitted any time except after midnight until 2 hours after each dose. Subjects can consume caffeinated beverages, which will be limited to no more than two 12 oz. portions a day except after midnight until 2 hours after each dose. Caffeine intake is not permitted on Cocaine infusion days (Study days -5, -2, -1, 11 and 12).

Exercise. Subjects will also be instructed to refrain from participation in contact sports and weight lifting from 48 hours before the inpatient period until completion of the study.

Tobacco Products. **Subjects will not be allowed to smoke during the study.**

Alcohol. Subjects will be questioned about their estimated daily intake of alcohol during the pre-study screening evaluation of eligibility. Any subject who shows physiological dependence on alcohol requiring medical detoxification will be excluded. Alcoholic beverages are not permitted from 48 hours before the inpatient period until the discharge from the study. Subjects will have a

breath analyzer test on admission. If a subject is found to be test positive for alcohol, the investigator or his designee may at his discretion decide if the subject should be rescheduled.

12 STUDY PROCEDURES

A time and events table summarizing the study procedures and assessments is provided in Appendix I.

12.1 Screening Procedures

Interested candidates between the ages of 18 and 45, inclusive, who report current use of cocaine, are not seeking treatment, and are available to participate in an inpatient study for about 30 days will meet with the investigator and receive an explanation of the study purpose and requirements. If still interested after receiving an explanation of the study, the candidates will be given an opportunity to review, inquire about, and sign the study informed consent form approved by the site's Institutional Review Board (IRB). After providing informed consent, the subject will participate in screening assessments.

Eight study subjects (6 receiving GBR 129092 and 2 receiving placebo) will be enrolled onto the study in one cohort at a time. Two study subject alternates for each cohort will be identified at the time the informed consent is obtained. These two alternates will complete the screening assessments and enter into the study if a study subject is dismissed for non-medical reasons.

The screening process will be done in stages at UTMB's GCRC. The first stage includes a complete physical examination, including vital signs (BP, HR, respiration rate, and temperature), and a 12-lead ECG. During the lead-in screening period (duration of up to 24 days before the inpatient period) the candidate subject will have an echocardiogram made by the study cardiologist. Noted pathology on either EKG or echocardiogram will be exclusionary. Other outpatient testing will include blood collection for hematologic, chemistries, alcohol, pregnancy, and infectious disease serology assessments. HRBS will be administered and HIV counseling has to be done prior to HIV blood draw. Urine will be collected for routine urinalysis. A urine drug toxicology screen will also be conducted for drugs of abuse. The urine drug toxicology screen must be negative with the exception of cocaine, cocaine metabolites, and marijuana to enroll in the study. Candidates deemed eligible based on the screening assessments mentioned above will enter the second stage of screening that will include administering a structured clinical interview (SCID) by a trained mental health professional, to determine if there are any underlining psychiatric conditions that might exclude the potential subject from participation. Before admission to the GCRC, subjects with positive urine drug toxicology will be allowed a three (3) to five (5) days-long washout period. To assure return with negative urine screens before admission, all subjects will receive payment for BE-negative urine screens and will not be permitted to initiate the inpatient phase until this is achieved.

Subjects will be instructed that no prescription/non prescription medications are to be taken within 14 and 7 days of the start of the study, respectively. Female subjects will also be instructed to not use oral contraceptives within 30 days prior to study participation. Subjects will also be instructed to refrain from using any alcohol from 48 hours before clinic intake until

discharge from the study. Subjects will also be instructed to refrain from participation in contact sports and weight lifting from 48 hours before the inpatient period until study completion.

Women of childbearing potential can be enrolled; however, appropriate contraception must be used throughout the study. No oral contraceptives, Depo-Provera, Norplant and intrauterine progesterone contraceptive system are to be taken or used within 30 days prior to the start of the study (in the case of DP or Norplant, if within the past 3 months). Double barrier contraception techniques or abstinence (starting at least 14 days prior to study) must be used until at least 14 days following the last dose of study drug. Appropriate methods include abstinence and the following double-barrier methods: diaphragm and condom (by the partner), intrauterine device and condom, or sponge and condom. If there is any question that a subject will not be reliable in the use of these double-barrier contraceptive methods, she will not be entered into the study.

Subjects must be informed of the unknown risks of becoming pregnant and must agree not to become pregnant during the time they are participating in this study.

Women participating in the study will be tested for serum beta-human chorionic gonadotropin (ß-HCG) to detect pregnancy at pre-intake screening, intake screening and within 72 hours prior to receiving the first dose of study drug. In the case of a positive or borderline serum ß-HCG pregnancy test at the (pre-)intake screening, the subject will not enter the study. Subjects will again be tested prior to discharge from the inpatient phase of the study and on follow up (day 48). In the case of a positive or borderline test at the end of the inpatient period, the NIDA clinical monitor will be contacted and the pregnancy will be recorded as an adverse event. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been terminated or completed. The outcome of the pregnancy will be reported to the NIDA clinical monitor without delay within 24 hours if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The result of each pregnancy test will be recorded on a CRF.

12.2 Intake Screening

Potential candidates whose screening assessment results do not exclude them from study participation will complete intake procedures and reside full-time as inpatients until discharge or completion of the study. Screening procedures after intake will be completed on the days -7 or -6 before first cocaine infusion and include brief physical exam, vital signs, 12 hour 12-lead ECG, urine drug toxicology screen, a ß-HCG (pregnancy test), a breathalyzer test, and BSCS, BPRS, BDI, BSI, POMS, ASI-Lite, VAS, BIS and IMT/DMT assessments.

EKGs provide some data on cardiac function but are limited in determination of specific anomalies that might be problematic for subjects in this study. Therefore, an echocardiogram evaluation will be conducted before intake. Echocardiographic evidence of left ventricular hypertrophy is well documented in chronic cocaine use (Brickner et al. 1991; Bertolet et al. 1990) and has been associated with an increased risk of cardiovascular events and increased mortality in several studies (Levy et al. 1990; Casale et al. 1986; Levy, Anderson et al. 1987; Levy, Phlen et al. 1987; McLenadian et al. 1987). It has been speculated that left ventricular hypertrophy in cocaine abusers provide a substrate that facilitate the development of

cardiovascular events, including myocardial ischemia and arrythmias. Left ventricular hypertrophy is associated with decreased coronary flow reserve, decreased subendocardial perfusion, and increased myocardial oxygen consumption, factors that may favor the development of myocardial ischemia in the setting of cocaine-induced coronary artery vasoconstriction and thrombosis. Furthermore it has been postulated that cocaine induced cardiac arrythmias are more likely to occur in the setting of underlying myocardial abnormalities such as infarction, ischemia, or contraction band necrosis. Thus, left ventricular hypertrophy may provide an anatomic substrate that potentiates the arrhythmogenic properties of cocaine.

Cocaine induced dilated cardiomyopathy is a recognized complication of chronic cocaine use (Chakko et al. 1992; Weiner et al. 1986; Duell et al. 1987; Bertolet et al. 1990; Schiller et al. 1989). Patients may be asymptomatic and clinically unrecognized and unsuspected after routine examination (Bertolet et al. 1990).

A two dimensional echocardiogram will be performed on all patients prior to enrolling in the study. This will be performed in a standard manner as outlined by the American Society of Echocardiography. Standard views will be obtained from the left parasternal, apical and subcostal areas. The test is noninvasive, painless, and without risk to the patient. Calculation of chamber size, systolic function, left ventricular mass and assessment of wall motion abnormalities will be performed according to the recommendations for quantitation of the left ventricle by two-dimensional echocardiography. Patients with measurements outside the normal range (indexed for gender and body surface area) will be excluded from the study.

Documenting normal left ventricular size and systolic function and the absence of hypertrophy of the ventricle wall will exclude serious cardiac structural disease that may be missed if we rely on a normal surface electrocardiogram. We feel this screening test will decrease the risk of an adverse event occurring during the study. A consultant cardiologist will interpret echocardiograms.

12.3 Enrollment and Randomization

A prospective subject who meets all of the study inclusion criteria and does not meet any of the exclusion criteria may be enrolled onto the study and randomized. Subjects will be randomized within cohorts to receive either GBR 12909 (6 subjects) or placebo (2 subjects). The data-coordinating center will supply the Research Pharmacist with pre-coded envelopes with treatment assignments. At the end of day –1 after having completed the 2nd baseline infusion, the subjects will be randomized and the investigator or study coordinator will obtain the treatment assignment from the Research Pharmacist. The Research Pharmacist will dispense the coded bottle of investigational agents for the subject to the investigator.

12.4 Cocaine Infusion Sessions

12.4.1 Schedule

Intravenous cocaine infusions will be conducted according to the schedule shown in Table 1. Screening infusions (sessions #1 and #2) will be conducted during the same day (day -5). Baseline (sessions #3 and #4) and treatment (sessions #5 and #6) infusions will consist of two infusion sessions over two consecutive days (days -2 and -1 for baseline infusions and days 11

and 12 for treatment infusions) and will be conducted in a random saline/cocaine order (Table 1). During the screening and baseline infusion sessions, the subject's responses to cocaine without concomitant GBR 12909 or placebo administration will be assessed. During the treatment infusion sessions, the subject's responses to cocaine with concomitant GBR 12909 or placebo administration will be assessed.

Table 1. Cocaine Infusion Session Schedule

Study Phase	Session Number	Study Day	Infusion
Screening	Sessions 1 & 2	-5	20 mg cocaine followed by saline 2 hours later and then followed by 40 mg cocaine 2 hr later
Baseline	Session 3	-2	Saline/20 mg cocaine followed by 20 mg cocaine/saline 1 hr later
Baseline	Session 4	-1	Saline/40 mg cocaine followed by 40 mg cocaine/saline 1 hr later
Treatment	Session 5	11	GBR 12909/placebo followed by saline/20 mg cocaine 3 hr later and then followed by 20 mg cocaine/saline 1 hr later
Treatment	Session 6	12	GBR 12909/placebo followed by saline/40 mg cocaine 3 hr later and then followed by 40 mg cocaine/saline 1 hr later

12.4.2 Conduct of Cocaine/Saline Infusion Sessions

All subjects will receive cocaine infusions on five days: days -5, -2, -1, 11 and 12. Cocaine will be administered by i.v. push over 60 seconds by the study cardiologist. On day -5 (screening infusions #1 and #2 to determine eligibility), subjects will receive 20 mg cocaine i.v. followed 2 hours later by saline infusion and then 2 hours later by 40 mg cocaine i.v. Subjects will receive baseline cocaine infusions on two consecutive days, day -2 (session #3, 20 mg cocaine i.v.) and day -1 (session #4, 40 mg cocaine i.v.). Subjects will receive treatment cocaine infusions on day 11 (session #5, 20 mg cocaine i.v.) and day 12 (session #6, 40 mg cocaine i.v.); these infusions will be concurrent with GBR 12909 administration and thus examine the interactions.

For each baseline and treatment session, subjects will be randomly assigned (1:1 ratio) to receive either saline (at 10:00 a.m.) followed one hour later by cocaine or cocaine (at 10:00 a.m.) followed one hour later by saline in a double-blind fashion (subjects and research staff will be blinded). During the treatment sessions #5 and #6 (study days 11 and 12), subjects will take GBR 12909 in a fasting state at 7:00 a.m., fast another 2 hours until breakfast at 9:00 a.m. and after that will get the infusions at 10:00 a.m. and 11:00 a.m.

For a subject to receive the screening cocaine infusions (sessions #1and #2), s/he must have a drug toxicology screening that shows negative urine drug/metabolite levels for drugs of abuse (except marijuana) before conduct of cocaine infusion session. Subjects with positive urine drug toxicologies will be allowed a three to five day washout period before screening cocaine infusion (sessions #1 and #2). A washout period will precede admission with contingent payments based on providing BE-negative urine before intake; this will preclude non-productive inpatient days. The screening infusions are to ensure that volunteers safely tolerate the cocaine test doses.

The baseline cocaine infusions of 20 and 40 mg i.v. (sessions #3 and #4) are performed up to two days after screening cocaine infusions (sessions #1 and #2), when urine is negative for cocaine. The baseline infusions provide cardiovascular and psychological response data in the absence of the investigational agent GBR 12909. Only subjects safely tolerating both 20 mg and 40 mg of cocaine and who can distinguish between the psychoactive effects of these two doses, as assessed by Visual Analog Scale (VAS) scores, will continue in the study.

For all dosages of GBR 12909, subjects must take daily dose two hours before breakfast.

Before and after each i.v. infusion, the subjects' physiologic responses will be closely monitored using repeated HR, BP, and ECG readings. During infusion sessions #1 and #2 that will be conducted on the same day (day -5), BP/HR will be recorded at the following time points relative to infusions: -10, -8, -6, -4, -2, ("0" is 20 mg cocaine i.v., no HR/BP), 2, 4, 6, 8, 10, 15, 20, 25, 30, 35, 40, 50, 55, 60, 90, 110 ("120" is saline i.v., no HR/BP), 122, 124, 126, 128, 130, 135, 140, 145, 150, 155, 160, 170, 180, 210, 230 ("240" 40 mg cocaine i.v., no HR/BP), 242, 244, 246, 248, 250, 255, 260, 265, 270, 275, 280, 290, 295, 300 minutes and then every 30 minutes for the next five hours. ECG and HR will be monitored continuously from 15 minutes before to 60 minutes after each infusion. 12-lead ECG will be performed at –10 (baseline) before and at +8, 20, 30,110,128,140,150,230,248,260 and 270 minutes after each infusion. Subjects will be monitored for at least 1 hour after the 40 mg i.v. cocaine infusion by study personnel and staff, including a cardiologist who will participate in cocaine administration. Thereafter, nursing staff will monitor participants and take vital signs at first at half an hour and then at hourly intervals for a total of six hours after 40 mg i.v. cocaine infusion until vital signs revert to being within 10% of the baseline (Table 2).

During infusion sessions #3-6 that will be conducted on study days -2, -1, 11 and 12, respectively, BP/HR will be recorded at the following time points relative to infusions: -10, -8, -6, -4, -2, (first infusion, saline/cocaine i.v.), 2, 4, 6, 8, 10, 15, 20, 25, 30, 35, 40, 50, 55, (second infusion, cocaine/saline i.v.), 62, 64, 66, 68, 70, 75, 80, 85, 90, 95, 100,110, 115, 120 minutes and then every 30 minutes for the next five hours. ECG and HR will be monitored continuously from 15 minutes before to 60 minutes after first infusion and for the first 30 minutes after second infusion. 12-lead ECG will be performed at at –10 (baseline) before and at +8, 20,30,50,68,80, and 90 minutes after each infusion. Subjects will be monitored for at least 1 hour after the second infusion by study personnel and staff. Thereafter, nursing staff will monitor participants and take vital signs (BP, HR, respiration rate, and temperature) at first at half an hour and then at hourly intervals for a total of six hours after second infusion until vital signs revert to being within 10% of the baseline (Table 3).

The Visual Analog Scale (VAS), which assesses psychoactive response to cocaine, will be administered 15 min before and at 5, 15, 25, 35, 45, 65, 75, 85, 95 and 105 minutes after each cocaine/saline infusion, and will be continued every 30 minutes for as long as the symptoms remain. The scale will allow assessment of cocaine related "high" as well as dysphoric reactions to cocaine withdrawal.

12.4.3 Safety Precautions

A physician will perform the infusions and will be present at least 1 hour after the completion of the infusions. Thereafter, the physician will remain on the medical campus and be available by pager for prompt response, if needed, for at least four hours post-infusion. If a subject demonstrates a significant adverse reaction to cocaine, the cocaine administration will be halted, appropriate medical response will be implemented (see Appendix III), and the subject will be discontinued from the remainder of the study. To facilitate and assure safety a cardiologist will participate in administration and post cocaine dose observation. The BPRS will be performed within 1 hour of the completion of each infusion to assess possible acute psychosis due to cocaine.

12.4.4. Stopping Criteria for Further Cocaine Infusion

Cocaine intravenous administration will be discontinued if any of the following events occurs:

1. Systolic BP > 165 mm Hg;
2. Diastolic BP > 100 mm Hg;
3. HR > 130 bpm;
4. Behavioral manifestation of cocaine toxicity, e.g., agitation, psychosis, inability to cooperate with study procedures.

12.4.5 Stopping Criteria for Further Study Participation

Further participation of the subject is stopped if any of the following events occur:

1. Acute chest pain, shortness of breath;
2. Systolic BP > 180 mm Hg sustained for 5 minutes or more;
3. Diastolic BP > 120 mm Hg sustained for 5 minutes or more;
4. Heart rate > (220 - age x 0.85) bpm sustained for 5 minutes or more;
5. Neurological or psychiatric events (e.g., panic or psychosis);
6. A clinically significant ECG abnormality, such as:
   - ST segment elevations in two or more continuous leads of greater than 0.1 mV.
   - ST segment depression of greater than 1 mm that are flat or down-sloping at 80 msec after the J point.
   - New bundle branch block.
   - Mobitz II 2^0 or 3^0 heart block.
   - Atrial fibrillation or atrial flutter or activation of any tachyarrhythmia for greater than 10 seconds.
   - Three or more consecutive ectopic ventricular complexes at a rate of greater than 100 per minute.
7. Any condition that in the clinical judgment of the investigator is of sufficient magnitude to present a danger to the subject.

12.4.6 Volunteer Discontinuation

Subjects will be excluded or discharged if their behavior is disruptive, non-compliant with study procedures, or otherwise not consistent with remaining in the hospital.

12.4.7 Subject Discharge and Follow-Up

The subjects will be discharged from the hospital 7 days after the last infusion of cocaine (session #6) on day 20. Subjects will be requested to return for follow up weekly assessments for 1 month after the day of discharge.

12.4 8 Subject Compensation

Subject payment will be determined by IRB requirements. Subject payment will consist of payment for screening procedures, payment for all in-patient procedures, and final payment at the completion of the outpatient follow-up visits. Payments will be back-loaded to provide incentive for subjects to complete the outpatient follow-up.

Subjects will be reimbursed at a rate of approximately $6/study hour. This will include the 12 hour waking-monitoring periods as well as all periods during the pre-study screening evaluation and the post study follow-up. Subjects will also receive a supplemental payment for completing all study elements. Finally, subjects will be reimbursed for travel to/from the medical center during the evaluation and follow-up periods. Payment for the pre-study screening evaluation will be paid at entry to the UCRC. If a subject is unable to continue (must be discharged or chooses to leave) due to data obtained during the screening infusions or the ECG profile, payment for completing the initial screenings will be made at the time of discontinuation. Payment for completion of the inpatient period will be paid at discharge. Payment for follow-up will be paid at the last (fourth) follow-up visit unless the subject wishes to discontinue; the 'completion' payment will be also made at the last follow-up visit. Approximate payment table is presented below.

Study Period	Total Days	Total Hours	Payment	Payment Time
Preliminary evaluation	10 to 24	6	$ 36	
Repeated visits for drug screens	up to 4	4	$ 24	
Final evaluation before intake	1 / 2	2	$ 12	Evaluation or Inpatient End*
Hospital period pre-study test	3	30	$ 180	Evaluation End
Hospital period (study hours)	22	220	$ 1,320	Inpatient End
Follow-up days (once a week for 4 weeks)	1	10	$ 60	
Completion of all study activities			$ 200	Follow-up End
Total possible payment			$ 1,832	
*Subjects discharged at the end of screening will be paid at that time; subjects retained will receive all payment at discharge from the hospital.				

13 CLINICAL AND LABORATORY EVALUATIONS

A table summarizing the timing of the clinical and laboratory assessments to be conducted over the entire study period is shown in Appendix I.

13.1 Screening

Screening evaluations will be performed initially before clinic intake and then in the inpatient setting.

Screening Assessments Before Intake. The following evaluations will be performed before clinic intake and must be performed within 30 days prior to intake:

1. Informed Consent;
2. Locator Form;
3. Demographics Information;
4. Cocaine use for prior 30 days using timeline follow back method;
5. Urine drug toxicology screen (including all conducted to establish eligibility);
6. Medical history;
7. Physical examination and vital signs (BP and HR);
8. 12-lead ECG;
9. Echocardiogram;
10. Hematology;
11. Blood chemistry, including liver function tests;
12. Infectious disease serology;
13. Serum ß-HCG (pregnancy test);
14. Plasma alcohol;
15. Routine urinalysis;
16. SCID.
17. HRBS;
18. HIV counseling;

Inpatient Screening Assessments. The following evaluations will be performed after intake before the first cocaine infusion:

1. Vital signs (BP and HR);
2. 12-lead ECG;
3. Urine drug toxicology screen;
4. Breathalyzer test;
5. Serum ß-HCG (day –7 and day –2);
6. BDI, BSI, BPRS and POMS;
7. ASI-Lite;
8. BSCS;
9. VAS
10. BIS;
11. IMT/DMT;
12. Adverse Events daily.
13. Hematology (on day –7) followed by measurements once a week (day -1, 7, 14, 20, 27, 34, 41, 48) during study.

13.2 Evaluations Performed Daily or Every Other Day While Inpatient

1. Adverse Events will be monitored daily starting as soon as the subject signed the informed consent form;
2. 12-lead ECG will be done once daily on GBR medication days 1-10.
3. BSI, BDI, POMS and BSCS will be performed every other day.
4. ARCI will be performed on days 2, 4, 6, 8, 11, 13,15, 18 and on each follow up visit.

13.3 Evaluations Performed During Infusion Sessions

13.3.1 Evaluations Performed During Screening Infusions

Series of activities that occur on day -5 when screening cocaine infusion sessions are scheduled are shown in Table 2 below.

Schedule of activities flexibility: "actual times may deviate plus or minus up to 10 minutes from the schedule".

Table 2. Screening Cocaine Infusion Sessions Daily Schedule

Time-point	**Activity (occurs at all sessions unless otherwise indicated)**
9:00 a.m.	Breakfast
9:10 a.m.	BSI, BDI, POMS, BSCS
-15 min (9:45 a.m.)	Start continuous monitoring of ECG and HR VAS
-10 min	BP/HR, 12 lead ECG
-8 min	BP/HR
-6 min	BP/HR
-4 min	BP/HR
-2 min	BP/HR
Time 0 (10:00 a.m.)	**Inject 20 mg cocaine i.v. 1 min push**
2 min	BP/HR
4 min	BP/HR
5 min	VAS
6 min	BP/HR
8 min	BP/HR, 12 lead ECG
10 min	BP/HR, IMT/DMT
15 min	VAS, BP/HR
20 min	BP/HR, 12 lead ECG
25 min	VAS, BP/HR
30 min	BP/HR, 12 lead ECG
35 min	VAS, BP/HR
40 min	BP/HR
45 min	VAS, BPRS
50 min	BP/HR
55 min.	BP/HR
60 min	BP/HR, Stop continuous ECG and HR monitoring

Time-point	Activity (occurs at all sessions unless otherwise indicated)
65 min	VAS
75 min	VAS
85 min	VAS
90 min	BP/HR
95 min	VAS
105 min	Start continuous ECG and HR monitoring, VAS
110 min (-10 min)	BP/HR, 12 lead ECG
120 min (noon)	**Inject saline i.v. 1 min push**
122 min	BP/HR
124 min	BP/HR
126 min	BP/HR
128 min	BP/HR, 12 lead ECG
130 min	BP/HR, IMT/DMT
135 min	BP/HR
140 min	BP/HR, 12 lead ECG
145 min	BP/HR
150 min	BP/HR, 12 lead ECG
155 min	BP/HR
160 min	BP/HR
165 min	BPRS
170 min	BP/HR
180 min	BP/HR Stop continuous ECG and HR monitoring
210 min	BP/HR
225 min	Start continuous ECG & HR monitoring
230 min (-10 min)	BP/HR,12 lead ECG
240 min (2:00 p.m.)	**Inject 40 mg cocaine i.v. 1 min push**
242 min	BP/HR
244 min	BP/HR
246 min	BP/HR
248 min	BP/HR, 12 lead ECG
250 min	BP/HR, IMT/DMT
255 min	BP/HR
260 min	BP/HR, 12 lead ECG
265 min	BP/HR
270 min	BP/HR, 12 lead ECG
275 min	BP/HR
280 min	BP/HR
285 min	BPRS
290 min	BP/HR
295 min.	BP/HR
300min	BP/HR, Stop continuous ECG and HR monitoring
330 min	BP/HR
360, 390 and 420 min	BP/HR

Time-point	Activity (occurs at all sessions unless otherwise indicated)
450, 480 and 510 min	BP/HR
540, 570 and 600 min	BP/HR

13.3.2 Evaluations Performed During Baseline and Treatment Infusions

Series of activities that occur on days when baseline and treatment cocaine infusion sessions are scheduled are presented in Table 3 (those activities that do not occur at each infusion session are noted). Refer to Table 1 for the timing of the infusion sessions according to the study day. Note that not all activities occur at each infusion session. Again, there is some **Schedule of activities flexibility**: "actual times may deviate plus or minus up to 10 minutes from the schedule".

Table 3. Baseline and Treatment Cocaine Infusion Sessions Daily Schedule (Those activities that do not occur at each infusion session are noted)

Time-point	Activity (occurs at all sessions unless otherwise indicated)
6.00 a.m.	Insert catheters (left and right arm)
6:55 a.m.	Draw blood for GBR 12909 assay (sessions #5 & 6)
7.00 a.m.	**Administer GBR 12909/placebo** (sessions #5 & 6)
7:30 a.m.	Draw blood for GBR 12909 assay (sessions #5 & 6)
8:00 a.m.	Draw blood for GBR 12909 assay (sessions #5 & 6)
8:30 a.m.	Draw blood for GBR 12909 assay (sessions #5 & 6), ARCI (on sessions #4 and #5)
8:59 a.m.	Draw blood for GBR 12909 assay (sessions #5 & 6)
9.00 a.m.	breakfast
9:30 a.m.	Draw blood for liver function tests (sessions # 4 & 6) Draw blood for GBR 12909 assay (sessions #5 & 6)
-15 min (9:45 a.m.)	Start continuous monitoring of ECG and HR VAS
-10 min	BP/HR, 12 lead ECG
-8 min	BP/HR
-6 min	BP/HR, Draw blood for cocaine assay (#4 & 6)
-4 min	BP/HR
-2 min	BP/HR, Draw blood for GBR 12909 assay (sessions #5 & 6)
Time 0 (10:00 a.m.)	**Inject saline/cocaine i.v. 1 min push**
2 min	BP/HR
4 min	BP/HR, Draw blood for cocaine assay (#4 & 6)
5 min	VAS
6 min	BP/HR
8 min	BP/HR, 12 lead ECG
10 min	BP/HR, IMT/DMT
14 min	Draw blood for cocaine assay (#4 & 6)
15 min	VAS, BP/HR
20 min	BP/HR, 12 lead ECG
25 min	VAS, BP/HR
30 min	BP/HR, 12 lead ECG, Draw blood for cocaine assay (#4 & 6)

Time-point	Activity (occurs at all sessions unless otherwise indicated)
35 min	VAS, BP/HR
40 min	BP/HR, Draw blood for cocaine assay (#4 & 6)
45 min	BPRS, VAS
50 min (-10 min)	BP/HR, 12 lead ECG
55 min.	BP/HR
58 min	Draw blood for GBR 12909 assay (sessions #5 & 6)
59 min	Draw blood for cocaine assay (#4 & 6), Continue ECG and HR monitoring
60 min (11:00 a.m.)	**Inject cocaine/saline i.v. 1 min push**
62 min	BP/HR
64 min	BP/HR, Draw blood for cocaine assay (#4 & 6)
65 min	VAS
66 min	BP/HR
68 min	BP/HR, 12 lead ECG
70 min	BP/HR, IMT/DMT
74 min	Draw blood for cocaine assay (#4 & 6)
75 min	VAS, BP/HR
80 min	BP/HR, 12 lead ECG
85 min	VAS, BP/HR
90 min	Draw blood for cocaine assay (sessions # 4 & 6) BP/HR, 12 lead ECG
95 min	VAS, BP/HR
100 min	BP/HR, Draw blood for cocaine assay (#4 & 6)
105 min	Draw blood for liver function tests (session # 4 & 6) BPRS, VAS
110, 115 min	BP/HR
120 min	Draw blood for cocaine assay (sessions # 4 & 6), BP/HR, Stop continuous ECG and HR monitoring
150 min	Draw blood for cocaine assay (sessions # 4 & 6), BP/HR
180 min	Draw blood for cocaine assay (sessions # 4 & 6), BP/HR
210 min	BP/HR
240 min	BP/HR, Draw blood for cocaine assay (#4 & 6)
270 min	BP/HR
300 min	BP/HR Draw blood for cocaine assay (sessions # 4 & 6) Draw blood for GBR 12909 assay (sessions #5 & 6)
330 min	BP/HR
360, 390, 420 min	BP/HR
9 hours	Draw blood for GBR 12909 assay (sessions #5 & 6)
21, 45, 69, 93 and 117 hours	Draw blood for GBR 12909 assay (session #6)

13.4 Evaluations at Discharge

The subjects will be discharged from the hospital 7 days after the last infusion of cocaine (session #6) on day 20. The following evaluations will be performed at time of discharge; the same evaluations will be performed in the case of early study discontinuation.

1. Vital signs (BP and HR);
2. Hematology;
3. Blood chemistries, including liver function tests;
4. 12-lead ECG;
5. Serum ß-HCG (pregnancy test);
6. Urine drug toxicology screen;
7. BSI, BDI, POMS, BSCS
8. BIS;
9. IMT/DMT;
10. HRBS;
11. HIV counseling;
12. Adverse events.

Note: All subjects will receive counseling for HIV risk-taking behavior and availability of treatment for cocaine dependence before discharge from the hospital. Individuals who might want treatment will have the option of enrolling in a clinical trials protocol for treatment or receiving referrals to available treatment programs.

13.5 Evaluations at Follow-up

Subjects will return for weekly follow-up visits for 1 month after the day of discharge (days 27, 34, 41 and 48).

The following evaluations will be performed during follow-up visits on days 27, 34 and 41:

1. Vital signs (BP and HR);
2. 12-lead ECG;
3. Urine drug toxicology screen;
4. Adverse events.
5. Hematology
6. ARCI Scale

The following evaluations will be performed during final follow-up visit on day 48:

1. Vital signs (BP and HR);
2. Hematology;
3. Blood chemistries, including liver function tests;
4. 12-lead ECG;
5. Serum ß-HCG (pregnancy test);

6. Urine drug toxicology screen;
7. BIS;
8. IMT/DMT;
9. HRBS;
10. ARCI Scale
11. HIV counseling;
12. Adverse events.

Note: All subjects will receive counseling for HIV risk-taking behavior and availability of treatment for cocaine dependence during final follow-up visit. Individuals who might want treatment will have the option of enrolling in a clinical trials protocol for treatment or receiving referrals to a treatment of choice.

13.6 Clinical and Laboratory Assessment Methods

The following describes the methods to be used for collection of clinical and laboratory evaluations.

13.6.1 Intake Assessments

A variety of standardized psychosocial assessments and information will be collected during screening and intake in order to describe fully the characteristics of participants and in order to facilitate future contact for follow-up. Study personnel who will administer the questionnaires and interviews are extensively trained and experienced in working with a drug abusing population.

13.6.1.1 Addiction Severity Index (ASI)-Lite CF Version

The ASI-Lite CF version will be administered by a research staff member having at least a bachelor's degree in the social sciences or equivalent training and experience as determined by the principal investigator. The ASI-Lite is the interviewer's estimate of the severity of the subject's status in seven areas (medical, employment, drug use, alcohol use, legal, family/social, and psychological). Composite scores will be calculated according to the procedures described by McGahan *et al*. (1982) and Carroll *et al*. (1994). The Lite version is a shorter version of the ASI that still retains all questions used to calculate the ASI composite scores. The ASI-Lite will be completed after intake.

13.6.1.2 Cocaine Use by Timeline Follow Back Method

Detailed histories of cocaine use over the past 30 days prior to screening will be obtained using the timeline follow-back method. The timeline follow-back method was described and validated by Sobell *et al.,* (1986) for reporting alcohol use. It has also been found to be a reliable method for assessing the history of psychoactive substance use in drug-abusing populations (Fals-Stewart *et al.,* 2000).

13.6.1.3 SCID

This instrument will be administered during screening and serves to determine whether the subject meets the DSM-IV criteria for drug dependence and to rule out any major psychiatric disorders (e.g., affective disorders, schizophrenia).

13.6.1.4 Breathalizer Test

The breathalyzer or breath alcohol test will be administered at intake to assess recent alcohol use.

13.6.2 Medical Assessments

13.6.2.1 Physical Exam

A physical exam of the oral cavity, head, eyes, ears nose and throat, cardiovascular system, lungs, abdomen (liver/spleen), extremities, skin, neuropsychiatric mental status and sensory/motor status, musculoskeletal system and general appearance will be performed during screening. Height and weight will be recorded.

13.6.2.2 Medical History

To monitor the health of all potential study subjects, health profiles and medical history will be collected during screening.

13.6.2.3 Vital Signs

Vital signs to be assessed at intake include oral temperature, sitting blood pressure, pulse rate, respiratory rate, and standing blood pressure and pulse rate (standing 1 minute), and standing blood pressure and pulse rate (standing 3 minutes).

13.6.3 Eligibility Checklist

The Eligibility Checklist must be completed prior to enrollment and randomization. This information will be used to determine whether the patient may be enrolled in the study. This form will document final eligibility and, if applicable, the reason the subject was not enrolled in the study.

13.6.4 Urine Toxicology

Urine toxicology for marijuana, opiates, cocaine, and amphetamines will be monitored twice weekly, as documented by a qualitative urine test that detects all these compounds, during outpatient screening. Subjects with positive urine drug toxicology will be allowed a three (3) to five (5) days-long washout period before admission. To assure return with negative urine screens before admission, all subjects will receive payment for BE-negative urine screens and will not be permitted to initiate the inpatient phase until this is achieved. This test will be also performed at inpatient screening, at the time of discharge and at the follow-up visits.

13.6.5 Laboratory Tests

13.6.5.1 Hematology

Blood will be collected in anticoagulant containing vacutainer tubes (3 mL) for hematologic assessments. Analysis of hemoglobin, hematocrit, mean corpuscular volume, white blood cell count, differential white blood cell count and platelet count will be performed. Analyses will be performed in the local clinical laboratory. The laboratory performing these assessments will be either directly regulated by the College of Pathologists (CAP) or the Clinical Laboratory Improvement Act of 1988 (CLIA) or indirectly according to CLIA guidelines. The laboratory will need to provide a copy of current certification. Hematologic assessments will occur during

pre-intake screening, on day –7 followed by measurements once a week (day -1, 7, 14, 20, 27, 34, 41, 48) during study.

13.6.5.2 Blood Chemistries/Liver Function Tests

Blood will be collected in serum separation vacutainer tubes and serum separated according to standard procedures. Quantitative analysis will be performed for the following analytes: creatinine, blood urea nitrogen (BUN), glucose, creatinine phosphokinase (CPK), lactate dehydrogenase (LDH), and electrolytes (Na, K, Cl, HCO_3). Liver function tests will include total bilirubin, aspartate aminotransferase (AST/SGOT), alanine aminotransferase (ALT/SGPT), and alkaline phosphatase (ALP). The laboratory performing these assessments will be either directly regulated by CAP or CLIA or indirectly according to CLIA guidelines. The laboratory will need to provide a copy of current certification. Blood chemistries, including liver function tests, will be performed during screening, at discharge and at the final follow-up visit. In addition, liver function tests will also be conducted on days -1, 11 and 12.

13.6.5.3 Pregnancy Test

A blood-based pregnancy test designed to measure human chorionic gonadotropin will be performed during screening, during intake (2x), at discharge and at the final follow-up visit.

13.6.5.4 Infectious Disease Panel

Blood will be collected in a serum separation evacuated venous blood collection tubes (e.g., Vacutainer™) and serum separated according to standard procedures. Qualitative analysis reporting positive/negative results will be performed during screening for the following analytes: hepatitis B surface antigen, hepatitis C virus antibody and HIV types 1 and 2. An HIV test informed consent must be obtained before collecting blood for this test. A purified protein derivative (PPD) skin test for tuberculosis will be performed on intravenous abusers of any drug and if positive a chest x-ray is required to assess active tuberculosis. If the subject reports that s/he has been previously positive for the PPD test, the PPD test will not be performed and only a chest x-ray will be required. A rapid plasma reagin test (RPR) for syphilis will be also performed.

13.6.6 Methods for Assessment of Primary Outcome Measures

13.5.6.1 Primary Outcome Measures

The primary outcome measures are adverse events and cardiovascular responses (HR, BP, ECG measurements).

13.6.6.2 Adverse Events (AEs)

AEs will be assessed daily by an investigative staff nurse or physician starting as soon as the subject signed the informed consent. If an AE is reported to a nurse that requires medical attention, it should be reported to a study physician immediately. The investigator or study physician will assess subjects for any medical or psychiatric side effects. All AEs will be recorded on an AE CRF that is completed weekly.

13.6.6.3 Cardiovascular Assessments

Before and after each i.v. infusion, the subjects' physiologic responses will be closely monitored using repeated HR, BP, and ECG readings. Measures of HR and BP will always be

simultaneously recorded (paired). During infusion sessions #1and #2 that will be conducted on the same day (day -5), BP/HR will be recorded at the following time points relative to infusions: -10, -8, -6, -4, -2, (20 mg cocaine i.v.), 2, 4, 6, 8, 10, 15, 20, 25, 30, 35, 40, 50, 55, 60, 90, 110 (saline i.v. at 120 min), 122, 124, 126, 128, 130, 135, 140, 145, 150, 155, 160, 170, 180, 210, 230 (40 mg cocaine i.v. at 240 min), 242, 244, 246, 248, 250, 255, 260, 265, 270, 275, 280, 290, 295, 300 minutes and then every 30 minutes for the next five hours. ECG and HR will be monitored continuously from 15 minutes before to 60 minutes after each infusion. 12-lead ECG will be performed at –10 (baseline) before and at +8, 20, 30, 110, 128,140, 150, 230, 248, 260 and 270 minutes after each infusion. Subjects will be monitored for at least 1 hour after the 40 mg i.v. cocaine infusion by study personnel and staff. Thereafter, nursing staff will monitor participants and take vital signs at first at half an hour and then at hourly intervals for a total of six hours after 40 mg i.v. cocaine infusion until vital signs revert to being within 10% of the baseline (Table 2)

During infusion sessions #3-6 that will be conducted on study days -2, -1, 11 and 12, respectively, BP/HR will be recorded at the following time points relative to infusions: -10, -8, -6, -4, -2, ("0" is first infusion, saline/cocaine, no HR/BP), 2, 4, 6, 8, 10, 15, 20, 25, 30, 35, 40, 50, 55, ("60" is second infusion, cocaine/saline, no HR/BP), 62, 64, 66, 68, 70, 75, 80, 85, 90, 95, 100, 110, 115, 120 minutes and then every 30 minutes for the next five hours. ECG and HR will be monitored continuously from 15 minutes before to 60 minutes after both infusions. 12-lead ECG will be performed at –10 (baseline) before and at +8, 20, 30, 50, 68, 80, and 90 minutes after each infusion. Subjects will be monitored for at least 1 hour after the second infusion by study personnel and staff. Thereafter, nursing staff will monitor participants and take vital signs at first at half an hour and then at hourly intervals for a total of six hours after second infusion until vital signs revert to being within 10% of the baseline (Table 3).

13.6.7 Methods for Assessment of Secondary Outcome Measures

13.6.7.1 Secondary Outcome Measures

The secondary outcome measures include PK of study agent GBR 12909, PK of cocaine and BE, craving for cocaine assessed using BSCS, neuropsychological and mood and personality tests including BPRS, BSI, BDI, POMS, VAS, HRBS and specific GBR 12909 effects.

13.6.7.2 Blood Sample Collections for Pharmacokinetic Determinations

A schedule of blood collections and volumes is provided in Appendix II including collection of samples for cocaine and GBR 12909 blood levels for pharmacokinetic calculations.

An intravenous catheter will be inserted for each infusion session, and can be maintained in place for the two days of infusion sessions in one week, if the subject wishes. Two intravenous catheters will be placed for infusion sessions that involve repeated blood draws on days -1, 11, and 12, one will be for cocaine administration, the other for blood sample collection.

Samples will be collected for assessment of cocaine pharmacokinetics on days -1 and 12 (sessions #4 and #6) in 5 cc grey-stoppered Vacutainer™ tubes containing sodium fluoride and potassium oxalate. On day 12 there will be two infusions, one at minute '0' and one at minute 60 with times measured from first infusion. Therefore, blood for cocaine/BE PK determinations will

be collected at the following time points: -6 minutes prior to and after infusion at +4, 14, 30, 40, 59 (is also –1 for second infusion in session #6), 64, 74, 90, 100, 120, 150, 180, 240, and 300 minutes post first infusion. In order to assess study agent GBR 12909 pharmacokinetics, peak and trough levels, blood will be collected in heparin-containing green-stoppered Vacutainers™ on days 1, 3, 5, 8, 9, 10, 11, 12, 13, 14, 15, 16, and 17. Blood for GBR 12909 PK will be collected prior to GBR 12909 dosing on days 1, 3, 5, 8, 9 and 10 (trough levels), at approximately -0.5 min, 0.5, 1, 1.5, 2, 2.5, 3, 4, 8, and 12 hours after GBR 12909 dosing on day 11 and before the dose of GBR 12909 on day 12 and then at the following time points after the dose: 0.5, 1, 1.5, 2, 2.5, 3, 4, 8, 12, 21 (day 13), 45 (day 14), 69 (day 15), 93 (day 16), and 117 hours (day 17). Refer to Table 3 for details. Each sample (5 mL) will be centrifuged within 20 minutes of the blood collection at 3000 x g for 15 minutes to separate the plasma. The plasma will be transferred to polypropylene tubes and properly labeled. The samples will be stored at the -80°C storage unit at the GCRC **immediately** until shipment to the analytical laboratory for analysis (Details on plasma sample collection, handling and shipment see operations manual).

Samples will be collected during baseline 40 mg i.v cocaine infusion (session #4) and treatment cocaine infusions (session #5 and #6). Samples will be collected for assessment of cocaine pharmacokinetics on days for scheduled sessions #4 and #6 (days -1 and 12) and for GBR 12909 pharmacokinetics on days 1, 3, 5, 8, 9, 10, 11, 12, 13, 14, 15, 16, and 17. Total blood loss during the study will be 455 mL (Appendix II).

13.6.7.3 Subjective Responses

During and after the saline and cocaine infusions subjects' subjective responses will be closely monitored. They will be administered 15 minutes before, and at 5, 15, 25, 35, 45, 65, 75, 85, 95, and 105 minutes after each i.v. infusion. For this scale, subjects will report the degree to which they feel “any drug effect”, "high", “good effects”, “bad effects”, “like cocaine”, "desire for cocaine", "depressed", "anxious", “stimulated”, and “likely to use” on a continuous scale digitized between 0 to 100 for computing a score. In addition, they will be asked to answer the question: How much do you think this is worth in dollars. The ARCI will be administered on Day –1 for baseline measurement and on Days 2, 4, 6, 8, 11, 13, 15, 18 at one point between 7:30 AM and 9:00 AM and on all follow-up visits. The ARCI consists of 49 statements in a true/false format .

13.6.7.4 Brief Substance Craving Scale (BSCS)

The BSCS is a self-administered assessment that asks the subject to rate his or her craving for cocaine. The BSCS used for this study is a modification of the State of Feelings and Cravings Questionnaire (Mezinskis *et al.*,1998). If the subject is unable to self-administer this assessment (e.g. physical handicap, poor reading skills) study personnel can assist by reading the questions out loud to the subject and/or marking the subject's response on the CRF. However, study personnel are not to offer interpretations of the questions. Subjects will start the measure at baseline (inpatient screening) and

continue to complete this questionnaire on an every other day basis until the end of the inpatient period of the study.

13.6.7.5 Beck Depression Inventory (BDI)

The BDI is a 22-item self-report inventory that focuses on the subject's subjective feelings of depression and is sensitive to changes in feeling status. Subjects will start the measure at baseline (inpatient screening) and continue to complete this questionnaire on an every other day basis until the end of the inpatient period of the study.

13.6.7.6 Brief Symptom Inventory (BSI)

The BSI is a 53-item self-report clinical rating scale used to assess psychological distress. Subjects will start the measure at baseline (inpatient screening) and continue to complete this questionnaire on an every other day basis until the end of the inpatient period of the study.

13.6.7.7 Profile of Mood States (POMS)

The POMS is a questionnaire that measures dimensions of affect or mood. It consists of 65 adjectives to which the client responds according to a 5-point scale ranging from “not at all” to “extremely”. Subjects will start the measure at baseline (inpatient screening) and continue to complete this questionnaire on an every other day basis until the end of the inpatient period of the study.

13.6.7.8 Brief Psychiatric Rating Scale (BPRS)

The BPRS is an interview that may be administered by a trained research nurse and conducted either by remote video or in face-to-face format to evaluate the severity of subject’s psychopathology, including anxiety, depression and symptoms of schizophrenia. The BPRS may be dichotomized into subjective items based on patients’ verbal reports and objective items based on visual observation of patients’ behavior. The BPRS total score ratings serve as indicators of psychiatric comorbidity in drug-dependent subjects and as predictors of mental health services utilization. Subjects will start the measure at baseline and will be administered this interview on the days of all cocaine infusions within one hour of the completion of infusion (sessions #1-6), as an indicator of possible acute psychotic effects of cocaine.

13.6.7.9 HIV Risk-Taking Behavior Scale (HRBS)

The HRBS is a brief 12-item interview administered scale that examines behavior of intravenous drug users in both injecting and sexual behavior. HRBS and HIV counseling will be administered at baseline (pre-intake screening), at discharge and at the final follow-up visit.

13.6.7.10 Barratt Impulsiveness Scale (BIS-11)

This instrument is a 30 item questionnaire (Patton *et al.,* 1995), which has been used in several previous studies on impulsivity and aggression (Allen *et al.,* 1998; Cherek *et al.,* 1997). The BIS-11 will be used as one of the primary measures of impulsivity for all subjects. It will be administered at baseline (inpatient screening), at discharge and at the final follow-up visit.

13.6.7.11 Continuous Performance Test (CPT)

A popular measure of attentional capacity (or vigilance) is the Continuous Performance Task (CPT) (Rosvold *et al.,* 1956), which requires participants to respond selectively to a series of stimuli (e.g., abstract shapes, letters, or numbers) presented briefly and rapidly (typically

presentations and delays of less than 500 ms). Since its appearance, the CPT has been modified many times, but usually the subject responds to identify a single target stimulus (e.g., "0") or a series of target stimuli (e.g., "A" followed by "X"), which remains constant throughout a testing session. These CPT procedures have been used to identify and characterize attention deficits in a variety of subject populations, including attention deficit disorder in children and adults (Halperin *et al.,* 1991), schizophrenics and persons at-risk for schizophrenia (Nuechterlein *et al*., 1994), as well as persons with learning disabilities (Dykman *et al.,* 1979, Swanson, 1981).

The CPT yields several key data, each parameter believed to evaluate different components of attentional processing. Three primary measures are used. First, omission errors (or misses) are failures to respond to a target stimulus. Most researchers agree that these errors represent deficits in sustained attention or vigilance. Second, commission errors (or false alarms) are responses made to stimuli other than target stimuli. Researchers have varied in both the way they have defined commission errors (in various paradigms) and in the interpretation of these errors. Some have suggested that commission errors represent impulsive responding (Halperin *et al.,* 1991, O'Dougherty *et al*.,1984; Sostek *et al*., 1980; Sykes *et al.,* 1971), however, others disagree with this interpretation (Wohlberg and Kornetsky, 1973). And third, latencies are the delay between the onset of a stimulus and the participant's response. Latencies provide information about the temporal requirements for processing information (Dougherty *et al.,* 2000; Halperin *et al*., 1988, 1991), indicate how difficult a discrimination is in a particular CPT task, and may also give an indication about how different populations process stimuli before responding (Halperin *et al.,* 1988, 1991). There are several versions of the CPT, which have been used in prior studies. The version, which will be used in this study, was developed and programmed for use in Windows 9; in each testing session of this version, the two task conditions, e.g. Immediate Memory Task/Delayed Memory Task (IMT/DMT), alternate in 5 min testing blocks with a 30 s rest period preceding each block. The IMT is always first and alternates with the DMT, with each presented twice. As a result, testing sessions last exactly 22 minutes. Both tasks are described below.

13.6.7.12 Immediate Memory Task (IMT)

This task was designed to measure brief attention capacity. A series of 5-digit numbers (e.g., 73021) are displayed on the monitor for 0.5 s and separated by a 0.5 s blackout period. Each of the digits measures 2.0 cm wide x 3.3 cm high, and the numbers are presented on the computer monitor in black on a white background. There are several distinct types of stimuli presented and types of responses that can be made. Subjects are instructed to respond on the computer's left mouse button when a 5-digit number (the target stimulus) appears that is exactly like the preceding stimulus. The probability of a target stimulus is set at 33%. A response made while a target stimulus appears on the monitor, or made before the next stimulus appears (1.0 s total), is recorded as a correct detection (or "hit"). A failure to respond to a target stimulus is recorded as an omission error (or "miss"). In addition to target stimuli, there is a 33% probability that a catch stimulus will appear. A catch stimulus is a number that differs from the preceding number by one of the five digits (its position and value is determined randomly). Responses (errors) made to catch stimuli are considered commission errors (or "false alarms"). Novel stimuli (numbers) which are not either target or catch trials (34% of the stimuli) are called filler stimuli

and responses made to these stimuli are called random errors. Commission errors on the IMT will be used as a laboratory measure of impulsivity.

13.6.7.13 Delayed Memory Task (DMT)

This task was designed to measure a subject's ability to retain and subsequently identify a stimulus kept in memory for longer periods of time. The primary difference between this task and the IMT is that all stimuli (including target, catch and filler) are separated by the number "12345", which is repeated three times at the same rate and duration as all other stimuli. For example, one possible sequence involving a target stimulus would be: 39863, 12345, 12345, 12345, and 39863. Subjects are instructed to ignore the "12345" and only to remember and identify stimuli separated by the series of "12345" numbers. These stimuli, "12345", are designated as distracter stimuli. Presenting these distracter stimuli allows us to increase cognitive load and to control for rates of visual stimulus presentation. In addition to the number of responses made to each type of stimulus, response latencies for correct detections and commission errors are recorded in milliseconds.

The IMT and DMT tasks are similar to the "n-back" sequential letter memory test (Gevins *et al*., 1990) because there is a contrast between a longer working memory delay period (DMT) and a shorter delay period (IMT), analogous to 2-back *versus* 1-back respectively. In addition, the IMT/DMT is similar to versions of n-back that require a motor response to occur after every stimulus, thus keeping the rate of motor behavior (and rate of visual stimuli) constant during the long and short delay condition. IMT/DMT is different from n-back in that IMT/DMT allows the experimenter to manipulate task difficulty independently of the duration of the working memory delay. In n-back, task "load" or difficulty is increased by increasing how far back in the sequence that the subject is required to remember (e.g., 3-back instead of 2-back), which increases the duration of the working memory delay. This is similar to the presentation of 2 different memory delay periods with DMT and IMT. IMT/DMT also varies working memory demand by changing the number of digits per stimulus to alter task difficulty independently from changing the working memory delay. Thus, both the memory delay and the number of digits per stimulus can be varied parametrically.

13.6.8 Concomitant Medications

Concomitant medications will be assessed once per week by an investigative staff member. Any medications to be taken during the study must be approved by the site principal investigator/study physician.

13.6.9 Discharge Form

The Discharge CRF will document all data relevant to subject discharge: reason for discharge; date of discharge; and study day of discharge.

14 REGULATORY AND REPORTING REQUIREMENTS

14.1 Good Clinical Practices

This study will be conducted in accordance with the most current version of the International Conference on Harmonization Guide for Good Clinical Practices (GCP). An Operations Manual will be provided to all investigational sites as a study quality assurance tool.

14.2 FDA Form 1572

The investigator agrees to sign and submit a Statement of Investigator (FDA Form 1572) to the sponsor prior to initiating this study.

14.3 IRB Approval

Prior to initiating the study, the investigator will obtain written IRB approval to conduct the study. Should changes to the study protocol become necessary, protocol amendments will be submitted in writing to the IRB by the investigator for IRB approval prior to implementation. In addition, IRBs will approve all advertising materials used for subject recruitment and any educational materials given to the subject. Annual reports and progress reports will be submitted to the IRB annually or at a frequency requested by the IRB.

The investigator will ensure that a duly constituted IRB at the study site that conforms with FDA regulations (21 CFR part 56) will review the protocol and the volunteer informed consent form. Each investigator will follow IRB and FDA guidance regarding reporting of adverse events. Each investigator will promptly report to the IRB all changes in research activity and all unanticipated problems involving risks to human subjects or others and will not make any changes in the protocol without IRB approval, except where necessary to eliminate immediate hazards to human subjects. Following procedures outlined by the IRB, each investigator will describe the study, its risks and benefits, to each subject and ensure that each subject understands the study prior to obtaining the subject's signature. A copy of the consent form will be given to the subject.

14.4 Informed Consent

All potential candidates for the study will be given a current copy of the Informed Consent Form to read. The investigator or other study physician will explain all aspects of the study in lay language and answer all of the candidate's questions regarding the study. If the candidate desires to participate in the study, s/he will be asked to sign the Informed Consent. No study procedure will be performed prior to signing Informed Consent. Subjects who refuse to participate or who withdraw from the study will be treated without prejudice.

14.5 Risks and Benefit Assessment

The primary risks of this study are those of possible adverse reaction to the study drugs, cocaine and GBR 12909. There is extensive experience with these cocaine infusion procedures and they appear to be safe. The doses used are modest, the exposure periods to the agents are brief, the safety screening and monitoring are appropriate, and there have been no significant prior adverse events with these procedures. The primary finding of a recent NIDA-sponsored phase 1, dose escalation protocol incorporating 25, 50, 75, and 100 mg daily dosages of GBR 12909 was a

slight increase in heart rate and systolic blood pressure in the majority of subjects at the higher doses (75 mg and 100 mg); this slight increase in HR and BP did not completely revert to baseline between successive dose levels (NIDA Communication, 2001). ECG effects of GBR 12909 were not significant at the dosages examined. No significant safety issues appeared from the psychometric data at any of the 4 tested doses of GBR 12909 (25, 50, 75 or 100 mg). There were no serious adverse events or dose-limiting toxicity. It is possible that the dopaminergic activities of cocaine and GBR 12909 might be additive or potentiated when they are administered together. The ascending order of cocaine doses is one protection against this risk. There is an extremely limited risk of a breach of confidentiality regarding study records, but this is unlikely, since staff is well trained and experienced in this area and all the mechanisms to assure confidentiality are in place. Notably, the team at **UTMB's GCRC** has extensive training and experience as well as extensive precautions in place. All requests for release are discussed with Dr.Cunningham/Dr.Grabowski and decisions made based on the evidence, often in consultation with GCRC staff members.

The study does not offer direct therapeutic benefit to participants. But, because it is directed toward the identification and development of effective treatment for cocaine abuse, it does offer the potential of future benefit to this same population group.

Overall, we believe that the risks are modest, that appropriate precautions have been taken, that there is potential societal health benefit, and that therefore the risk/benefit ratio is favorable.

14.6 Drug Accountability

Upon receipt, the investigator/pharmacist or a licensed designate is responsible for taking inventory of the investigational agents. A record of this inventory must be kept and usage must be documented. Any unused or expired investigational agents shall be returned to the study sponsor.

14.7 Outside Monitoring

Compliance With NIDA Policy On Monitoring Plans: In June 2000, the National Institutes of Health (NIH) issued a policy that extended the requirement for inclusion of monitoring plans to phase 1 and 2 clinical trials. (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html) That Further Guidance followed the policy issued in June 1998 on data and safety monitoring (http://grants.nih.gov/grants/guide/notice-files/not98-084.html), which required the establishment of Data and Safety Monitoring Boards (DSMBs) for all NIH-supported or -conducted multi-site clinical trials involving interventions that entail potential risk to the participants. NIH requires each Institute to have a system of oversight of the conduct of clinical trials to ensure the safety of participants and the validity and integrity of the data.

This protocol is in compliance with that policy. The procedures for reporting Serious Adverse Events (SAEs) to NIDA, the IRB and FDA are contained under section 14.8. A DSMB will be reviewing the final data and safety profile from this trial.

Note: Each cohort of 8 subjects will complete all inpatient study procedures and be released from the clinic before starting the next cohort. Prior to initiating dosing of the next cohort, the safety

data of the completed cohort including vital signs, the ECG parameters (not limited to prolongation of the QT interval) and adverse events will be reviewed by the NIDA medical monitor, study-independent physician and a physician representative of the governing Institutional Review Board (IRB) for a determination to proceed to dosing of the next cohort. Dosing will start at the lowest dose of GBR 12909 (50 mg) and escalate to the next higher doses sequentially (75 then 100 mg).

Medical Monitor: A medical monitor will be appointed for the study. The medical monitor will be responsible for establishing concurrence with the investigator on the severity of any SAEs, the relatedness to the study treatments, and for determining if the SAE should be reported to the FDA in a 7 or 15 day expedited report or an annual report. The medical monitor will also be responsible for tracking and assessing trends in the SAEs reported.

Clinical Monitors: All investigators will allow representatives of the sponsor to periodically audit, at mutually convenient times during and after the study, all source documents for each subject. The monitors will assure that submitted data are accurate and in agreement with source documentation; verify that investigational agents are properly stored and accounted for, verify that subjects' consent for study participation has been properly obtained and documented, confirm that research subjects entered into the study meet inclusion and exclusion criteria, and assure that all essential documentation required by GCP guidelines are appropriately filed.

Monitors will conduct a site initiation visit prior to the start of the study. At this visit, they will assure that proper study-related documentation exists, assist in training investigators and other site personnel in study procedures and compliance with good clinical practice guidelines and FDA regulations, confirm receipt of study supplies, and assure that acceptable facilities are available to conduct the study.

Routine monitoring visits by the sponsor's representatives will be scheduled at appropriate intervals but more frequently at the beginning of the study. At these visits, the monitors will verify that study procedures are being conducted according to the protocol guidelines. At the end of the study they will advise on storage of study records and return of unused study medication. The site should anticipate visits by sponsor, sponsor's representatives, NIDA, and the FDA.

14.8 Adverse Events Reporting.

In accordance with FDA reporting requirements, all AEs occurring during the course of the clinical trial will be collected, documented, and reported by the principal investigator or sub-investigators according to the specific instructions detailed in this section of the protocol and Appendix IV.

An AE is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial, whether or not the event is considered medication-related or clinically significant**.** For this study, AEs will include events reported by the subject, as well as clinically significant abnormal findings on physical examination or laboratory evaluation. A new illness, symptom, sign or clinically significant clinical laboratory abnormality or worsening of a pre-

existing condition or abnormality is considered an AE. Stable chronic conditions, such as arthritis, which are present prior to clinical trial entry and do not worsen are not considered AEs.

All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed by study investigators until satisfactory resolution. AEs should be reported up to 4 weeks following completion of, or termination from treatment.

14.9 Serious Adverse Events

Each adverse event or reaction will be classified by the study investigator as serious or non-serious. Based on the seriousness of the adverse event or reaction appropriate reporting procedures will be followed. The International Conference on Harmonization (ICH) Guideline for Industry: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, ICH-E2A March 1995, as implemented by the U.S. Food and Drug Administration defines serious adverse event (SAE) or reaction as any untoward medical occurrence that at any dose:

- results in death;
- is life-threatening; *(NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.)*
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity; or
- is a congenital anomaly/birth defect.

An unexpected event is one that is not described with respect to nature, severity, or frequency in the current Investigator's Brochure.

Any SAEs due to any cause that occur during the course of this investigation, whether or not related to the investigational agent, must be reported within 24-hours by telephone to: the Study Medical Monitor and the IND sponsor. The telephone report is to be followed by submission of a completed SAE Form with demographic information and a narrative explanation of the event. Attached to the SAE Form should be photocopies of the AE Form, the Concomitant Medication Form, and the Medical History Form from the subject's CRFs. All serious medical events are also to be reported to the responsible IRB according to local regulatory requirements. All participating investigators will be notified of any serious and unexpected AE requiring submission to the FDA in an IND safety report from the sponsor.

Any fatal or life-threatening SAE that is investigational agent related and unexpected must be reported by the sponsor initially to the FDA within 7 calendar days via telephone, facsimile or e-mail. A follow-up written report must be submitted in 8 days to the FDA. All AEs that are both serious and unexpected but not life threatening or lethal must be reported to the FDA, in writing,

within 15 calendar days of notification of the sponsor of the SAE. All other SAEs will be reported in an annual report or more frequently as necessary. Any additional clinical information that is obtained must be reported to the FDA, as it becomes available in the form of an information amendment. The sponsor will inform NIDA of all SAEs that occur during the study.

There can be serious consequences including ultimately, criminal and/or civil penalties for sponsors who fail to comply with FDA regulations governing the reporting of SAEs to FDA. The study investigators in this study have the responsibility of promptly reporting all SAEs to the sponsor in order that the sponsor can comply with these regulations.

If a study subject withdraws from the study or if an investigator decides to discontinue the subject from the study because of a SAE, the subject must have appropriate follow-up medical monitoring. If the subject is hospitalized, medical monitoring will consist of not less than daily evaluation by physical examination, vital signs, laboratory evaluations, and if applicable, ECG monitoring for significant treatment-emergent abnormalities. Monitoring will continue until the problem prompting hospitalization has resolved or stabilized with no further change expected or is discovered to be clearly unrelated to study medication or progresses to death.

15 ANALYTICAL PLAN

15.1 Outcome Measures

15.2 Primary Outcome Measures

The primary outcome measures are adverse events and cardiovascular responses (HR, BP, ECG).

15.3 Secondary Outcome Measures

Secondary outcome measures are intended to determine if there are any changes in GBR 12909 or cocaine pharmacokinetics and to assess the effects of GBR 12909 on a variety of neuropsychological measures. Secondary outcome measures include:

1. PK parameters of cocaine and BE including:
   - AUC — Area under the plasma concentration time-curve
   - C_{max} — Maximum observed concentration
   - T_{max} — Time for maximum concentration
   - k_e — Elimination rate constant (if data permit)
   - $t_{1/2}$ — Terminal half-life (0.693/(z))
   - CL — Clearance determined by the formula $CL=Dose/AUC_{0-24}$ (if data permit)
   - V_d — Volume of distribution (if data permit)
2. PK of study agent GBR 12909 (peak-, trough levels, Cmax, CL/F (apparent clearance), and AUC (0-24) for day 11 and day 12, and $t_{1/2}$ for the last dose)
3. Craving for cocaine, assessed using BSCS
4. Psychological assessments including VAS
5. Mood and personality assessments (BPRS, BSI, BDI, POMS, HRBS, BIS and IMT/DMT)

15.4 Analysis Plan

15.4.1 Primary Outcome Measures

HR and BP measures during saline infusions will be compared to HR and BP after each cocaine infusion (20 mg and 40 mg doses). Changes in HR and BP induced by cocaine infusion along with GBR 12909 will be compared to those without GBR 12909, by cocaine dose level (20 mg and 40 mg doses), using repeated measures analysis of variance (ANOVA).

Changes in ECG readings during saline infusion as compared to those taken during cocaine infusions will be reported as summary statistics.

Adverse event data will be compiled for GBR 12909 and placebo cohorts and presented as summary statistics.

15.4.2 Secondary Outcome Measures

Plasma concentration-time profiles of cocaine after baseline cocaine infusion (session #4) will be analyzed to obtain pharmacokinetic parameter estimates of cocaine ($T_{max,}$ AUC, apparent $t_{½}$, CL, V_d, and k_e) by individual and the means computed (between subjects comparison) will be compared with data from the post-treatment cocaine infusions for each GBR 12909 dose level (sessions #5 and #6 for 50 mg GBR 12909 level in the first cohort, for 75 mg GBR 12909 level in the second cohort, and for 100 mg GBR 12909 level in the third cohort) being averaged by subject. Blood for cocaine/BE PK determinations will be collected at the following time points: 6 minutes prior to and 4, 14, 30, 40, 59, 64, 74, 90, 100, 120, 150, 180, 240, and 300 minutes post infusion (sessions #4 and #6).

Blood collected prior to GBR 12909 dosing will provide the GBR 12909 trough levels.
PK parameters determined for treatment infusions (session #6) will be compared between GBR 12909 dose levels by statistical analysis.

Sample collections for GBR 12909 PK determinations will be as follows:
Collection schedule on days 1, 3, 5, 8, 9 and 10: approximately -0.5 min, 0.5 hour after GBR dosing, 1 hour after, 1.5 hours, 2, 2.5, 3, 4, 8, and 12 hours after GBR 12909 dosing.
On days 11 and 12: Samples will be taken at the following time points before and then after GBR 12909 dosing: -0.5 minutes, 0.5 hour after GBR dosing, 1, 1.5, 2, 2.5, 3, 4, 8, 12 hours after.
Further, one PK sample for GBR is taken at 7 a.m. on days 13 (24 hours after last GBR dosis) day 14 (48 hours after last GBR dosis), day 15 (72 hours after last dosis), day 16 (96 hours after last dosis) and day 17 (120 hours after last dosis).
Pharmacokinetics (peak and trough levels) of GBR 12909 during treatment at a dose of 50 mg, 75 mg and 100 mg will be determined. These data will be compared to PK of GBR 12909 obtained during the treatment cocaine infusions for each dose level, i.e. sessions #5 and #6 for 50 mg GBR 12909 level in the first cohort, 75 mg GBR 12909 level in the second cohort, and 100 mg GBR 12909 level in the third cohort, by statistical analysis.

Psychological outcome measures (VAS) obtained during saline infusions will be compared between GBR 12909 and placebo cohorts to those during cocaine infusions by cocaine dose level

to determine the extent to which these measures are modified by the administration of GBR 12909 using repeated measures ANOVA.

Changes in BSCS, BSI, BDI, POMS, BPRS, HRBS, BIS, ARCI and IMT/DMT scores will be compared before and after GBR 12909 administration using repeated measures ANOVA or generalized estimating equations.

Population demographics will be tabulated for both treatment cohorts (GBR 12909 and placebo) and presented in a tabular form.

16 DATA MANAGEMENT AND CASE REPORT FORMS

16.1 Data Collection

Data will be collected at the study sites on source documents which will be entered at the site into paper case report forms (CRFs) from a local source document. The CRFs will be supplied by the NIDA data coordinating center. CRFs are to be completed on an ongoing basis during the study. The medical chart and the source documents are the source of verification of data. CRFs should be completed according to the instructions in the study operations manual. The principal investigator is responsible for maintaining accurate, complete and up-to-date records for each subject. The principal investigator is also responsible for maintaining any source documentation related to the study, including any films, tracings, computer discs or tapes.

16.2 Data Editing and Control

Data received at the NIDA data coordinating center will be reviewed. If incomplete or inaccurate data are found a data clarification request will be forwarded to the site for a response. The site will resolve data inconsistencies and errors prior to returning data to the data coordinating center.

All corrections and changes to the data will be reviewed prior to being entered into the main study database. NIDA/DTR&D and the participating site will receive reports at least monthly regarding the quality and quantity of data submitted to data coordinating center.

Participating investigators agree to routine data audits by the sponsor's designated staff, audits by the staff of the NIDA datacoordinating center and by NIDA's programmatic staff. Monitors will routinely visit the site to assure that data submitted on the appropriate forms are in agreement with source documents. They will also verify that study agents have been properly stored and accounted for, subject informed consent for study participation has been obtained and documented, all essential documents required by GCP regulations are on file, and the site is conducting the study according to the research protocol. Any inconsistencies will be resolved, and any changes to the data forms will be made using the established procedures specified in the study Operations Manual.

16.3 Data Entry, Processing, and Analyses

Data will be collected at the study sites on source documents which will be entered into CRFs. When the study is completed and all data have been entered into the clinical database and the database has been checked by Quality Assurance and is locked, analysis of the data will be

performed by the data coordinating center in accordance with the analytical plan section of this protocol. Periodically, during the investigation, data sets will be submitted to the NIDA DTR&D central data repository according to procedures specified in the study operations manual.

16.4 Study Documentation and Records Retention

Study documentation includes all CRFs, data correction forms, workbooks, source documents, monitoring logs and appointment schedules, sponsor-investigator correspondence and regulatory documents (e.g., signed protocol and amendments, Ethics or Institutional Review Committee correspondence and approved consent form and signed subject consent forms, Statement of Investigator form, and clinical supplies receipt and distribution records).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study. Accordingly, source documents include, but are not limited to, laboratory reports, ECG tracings, X-rays, radiologist reports, patient diaries, biopsy reports, ultrasound photographs, patient progress notes, hospital charts or pharmacy records and any other similar reports or records of any procedure performed in accordance with the protocol.

Whenever possible, the original recording of an observation should be retained as the source document; however, a photocopy is acceptable provided that it is a clear, legible, and an exact duplication of the original document.

Government agency regulations and directives require that the investigator must retain all study documentation pertaining to the conduct of a clinical trial. These documents must be kept for a minimum of six years after discontinuation of the IND or 6 years after the approval of the NDA.

16.5 Confidentiality

16.5.1 Confidentiality of Data

Particular attention is drawn to the regulations promulgated by the Food and Drug Administration under the Freedom of Information Act providing, in part, that proprietary information furnished to clinical investigators and Institutional Review Boards will be kept confidential by the Food and Drug Administration only if maintained in confidence by the clinical investigator and Institutional Review Board.

By signing this protocol the investigator affirms to NIDA that information furnished to the investigator by NIDA will be maintained in confidence and such information will be divulged to the Institutional Review Board, Ethical Review Committee, or similar or expert committee; affiliated institution; and employees only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees.

16.1.2 Confidentiality of Patient Records

To maintain subject confidentiality, all laboratory specimens, CRFs, reports and other records will be identified by a coded study subject number only. Research and clinical records will be stored in a locked cabinet. Only research staff and NIDA program officials will have access to

the records. Subject information will not be released without written permission, except as necessary for monitoring by the FDA, NIDA monitoring contractor or NIDA. Upon approval of the study by an IRB, an application will be filed with NIDA for a certificate of confidentiality.
By signing the protocol the investigator agrees that within local regulatory restrictions and ethical considerations NIDA or any regulatory agency may consult and/or copy study documents in order to verify case report form data.
The only people who will know the identity of the subjects are members of the research team and, if appropriate the physicians and nurses. No information about the subjects, or provided by the subjects during the research, will be disclosed to others without the subjects' written permission, except:

- if necessary to protect subjects' rights or welfare, or
- if required by law.

Authorization for protection of identity is now available to investigators engaged in research on the use and effect of psychoactive drugs under section 301 (d) of the Public Health Service Act, as amended by Public Law 93-282 (42 U.S.C. 241) (d) 0. "Such authorization affords the person to whom it is given a privilege to protect the privacy of research subjects by withholding the names or other identifying characteristics of such research subjects from all persons not connected with the conduct of the research. Persons so authorized may not be compelled in any federal, state, or local civil, criminal, administrative, legislative, or other procedures to identify such individuals," (Federal Register/Vol. 44, No. 66/Wednesday April 4, 1979/Rules and Regulations/Part VII.) The usual exemptions for audit and evaluation are allowed, but such auditors and evaluators would be bound to the same protections of subjects. The principal investigator has obtained a certificate of confidentiality. The provision of this authorization will be explained to all potential participants. Additional protection will be offered to our subjects in that identifying information will not be part of the data set and will not be available except on a need-to-know basis.

17 PUBLICATIONS OF THE STUDY RESULTS

Publications derived from this study will include input from the principal investigator, his or her colleagues, and NIDA personnel. Such input should be reflected in publication authorship, and agreement regarding order of authors should be established before writing a manuscript.

18 SIGNATURES

NIDA REPRESENTATIVE

Typed name(s)	**Signature**	**Date**
Roberta Kahn, M.D. NIDA Medical Monitor	_____	_____
Jurij Mojsiak, M.S. NIDA Project Officer	_____	_____
Ahmed Elkashef, M.D. NIDA Investigator	_____	_____
Nora Chiang, Ph.D. NIDA Investigator	_____	_____

INVESTIGATOR(S)

I agree to conduct this clinical study in accordance with the design and specific provisions of this protocol; deviations from the protocol are acceptable only with a mutually agreed upon protocol amendment with the IRB approval. I also agree to report all information or data in accordance with the protocol, and, in particular I agree to report any serious adverse experiences as defined in Section 14.8 of this protocol.

Typed name(s)	**Signature**	**Date**
Kathryn Cunningham,Ph.D. Principal Investigator	_____	_____
John Grabowski, Ph.D.	_____	_____
Jeff Matthews, MD Sub-Investigator	_____	_____
David Ware, MD Sub-Investigator	_____	_____
F. Gerrard Moeller, MD Sub-Investigator	_____	_____
R.Meisch,MDPhD Sub-Investigator	_____	_____

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Study Phase	**Pre-intake Screening**	**Intake Screening**	**Screening Infusions**	**Baseline Infusions**				**Treatment Infusions**		**Dis-charge**	**Follow-up**	
Study day	**-30 to -8**	**-7* & -6**	**-5**	**-2**	**-1**	**0**	**1-10**	**11**	**12**	**20**	**27(7), 34(14), 41(21)**	**48 (28)**
Informed consent	X											
Locator form/ Demographics	X					**RANDOMIZATION COMPLETED**						
Cocaine use by timeline follow back	X											
Breathalyzer test		X										
12-lead ECG	X	X	X	X	X		X	X	X	X	X	X
Echo Cardiology	X											
SCID	X											
Medical History/ Physical Exam/routine U/A	X											
ASI-Lite		X										
Vital Signs	X	X								X	X	X
Chemistries plus liver function tests	X									X		X
Liver Function Tests					X			X	X			
Hematology	**On days -30, -7, -1, 7, 14, 20, 27, 34, 41, 48.**											
Pregnancy Test	X[a]	**X[a]**		**X[a]**						X[a]		X[a]
Infectious disease serology	X											
Plasma alcohol	X											
Urine toxicology screen	X	X								X	X	X[a]
BSI, BDI, POMS, BSCS, ARCI		X[b]	X[b]		X[b]		X[b]	X[b]			X[b]	X[b]
BIS		X								X		X
HRBS and HIV counseling	X									X		X
GBR 12909 or placebo							X[c]	X[c]	X[c]			
GBR 12909 blood levels							X[c]	X[c]	X[c]			
Adverse Events	X	X	X	X	X		X	X	X	X	X	X
Cocaine Infusion Session #			**1-2**	**3**	**4**			**5**	**6**			
20 mg cocaine/saline/40 mg cocaine i.v.			X									
20 mg cocaine i.v.				X				X				
40 mg cocaine i.v.					X				X			
VAS		X	X	X	X			X	X			
Memory tests IMT/DMT		X	X	X	X			X	X	X		X
Continuous BP, HR, ECG monitoring			X	X	X			X	X			
BPRS		X	X	X	X			X	X			
Cocaine Blood PK					X				X			

APPENDIX I: Time And Events Schedule

*** Days –7 and - 6** are the days of inpatient screening.

X[a] - Pregnancy test should be done at pre-intake screening, intake screening, then within 72 hours before the first dose of **st**udy drug (day –2) and also at discharge and during final follow-up.

X[b] - BSI, BDI, POMS, BSCS will be performed at intake and then every other day- the last evaluation is on day of discharge. The ARCI Scale will be administered on Day –1 for baseline measurement and on Days 2, 4, 6, 8, 11, 13, 15, 18 at one point between 7:30 AM and 9:00 AM and on each follow-up visit. **X[c]** - Blood for GBR 12909 PK will be collected on days 1, 3, 5, 8, & 9 -17.

APPENDIX II: Schedule of Blood Collections

Analysis	Volume Per Sample	Type	Number of Samples per Day																	Total Volume
Study Day			Pre-intake Screening	-7	-1	1	3	5	8	9	10	11	12	13	14	15	16	17	20	48	
Chemistries plus liver function tests	10 mL	S	1																1	1	30 mL
Liver function tests	10 mL				2							2	2								60 mL
Hematologies	3 mL	WB	**On days -30, -7, 0, 7, 14, 20, 27, 34, 41, 48.**																		30 mL
Infectious disease serology	10 mL	S	1																		10 mL
PK Samples for cocaine	5 mL	P			15								15								150 mL
PK Samples for GBR 12909	5 mL	P				1	1	1	1	1	1	9	9	1	1	1	1	1			145 mL
Pregnancy Test	5 mL	S	1	1	1(at day -2) X[a]														1	1	25 mL
Alcohol Test	5 mL	P	1																		5 mL
Total																					**455 mL**

S = serum,
P = plasma;
WB = whole blood

APPENDIX III: Standard Operating Procedure for Management of Cardiovascular Complications During Cocaine Administration

I. SCOPE

This Standard Operating Procedure (SOP) provides guidelines for the management of cardiovascular complications during clinical trials involving cocaine infusion that are safe and effective for the medical emergency management of human subjects. Cocaine acts as a potent sympathomimetic agent through blockade of presynaptic reuptake of catecholamines, while simultaneously depressing cardiac conduction through its local anesthetic action as a sodium channel blocker. The simultaneous effects of cocaine administration include increased afterload, coronary vasoconstriction, and depressed conduction, resulting in cardiac stress and the potential for arrhythmias. In addition, experienced cocaine users who are recruited for these trials have been documented to have a high incidence of occult cardiac abnormalities. It is estimated that 54% of otherwise healthy chronic cocaine users have left ventricular hypertrophy, 50% have ST-segment elevation (early repolarization), and 33% have episodic ST-segment elevations during ambulatory monitoring (1).

These considerations suggest that specific protocols for treating hypertension, ECG changes, and arrhythmias associated with cocaine administration are warranted, based on available literature and recommendations of the American Heart Association (AHA) (2).

II. PHARMACOLOGIC CONSIDERATIONS

The peak action of intravenous (i.v.) cocaine administration occurs in 3-5 minutes. Because of rapid metabolism by plasma esterases, the effects of cocaine on heart rate and systemic pressure are expected to be short-lived (45-90 minutes); however, episodes of ischemia may be intermittent or delayed due to unpredictable episodes of coronary vasospasm. Initially, and especially after low-dose cocaine, sinus bradycardia may occur, but is unlikely to require treatment because it is soon succeeded by tachycardia.

III. EQUIPMENT AND MEDICATION SETUP

III.A. Setup

1. Equipment availability - the Infusion Unit shall have available one resuscitation bag, suction apparatus, two oxygen outlets, two compressed air outlets, humidifiers, heated nebulizers and one bedside monitor for ECG, respiratory efforts, blood pressure (by finger plethysmography or FinaPress), and pulse oximetry.
2. In addition, this Unit will have an intubation tray and crash cart with ECG, defibrillator and pacemaker.
3. Medications will be located in the locked medication cabinets and crash cart.

4. The integrity of the emergency equipment and drugs will be checked by the Nursing Staff every 24 hours. In addition, the Pharmacy Service will check expiration dates on all medications in the Infusion Unit on a monthly basis.

III.B. Safety and Maintenance

1. General safety rules throughout the hospital shall apply in the Unit.
2. Electrical preventive maintenance and safety program and medical equipment maintenance will be conducted according to the Hospital Acute Care Unit Policy and Procedures.

IV. PROCEDURES

IV.A. Hypertensive Crises

Recognition: Elevated blood pressure (BP) levels (Diastolic > 120 mm Hg, Systolic > 180 mm Hg) or elevated BP associated with encephalopathy, stroke, acute aortic dissection, acute left ventricular failure, or myocardial ischemia will be deemed hypertensive emergencies.

Treatment: Stop cocaine infusion then administer treatment. The safest first-line treatment of hypertension due to cocaine is sedation with a short-onset benzodiazepine, such as midazolam. Benzodiazepines control agitation and elevate the seizure threshold. Midazolam, 1-5 mg i.v. incrementally is unlikely to cause apnea. Oxygen should be administered at the same time. Intravenous vasodilators that act by alpha-blockade or other mechanisms can be safely used. All agents should be rapid in onset and rapidly titratable. Alternatively, give Lorazepam 2 mg i.v. push followed by reduction of BP with combined alpha and beta adrenergic receptor antagonist, labetolol, 20 mg i.v.over 5 minutes with repeat infusions every 20 minutes if necessary. Subsequent doses should be calculated on the basis of the diastolic response. Calcium channel blockers can be used, and have the advantage of elevating the ventricular fibrillation threshold.

Beta-blockers, such as esmolol and propranolol, should be avoided because their use can result in myocardial depression (3) and unopposed coronary vasoconstriction (4). Labetalol is a relatively weak alpha-blocker, and experimentally it does not relieve coronary vasospasm (5). The ratio of beta:alpha antagonism is 7:1. However, there is clinical experience with labetalol's safety in this application, and the AHA handbook lists it for emergency cardiac care for the treatment of cocaine intoxication.

Benzodiazepines:	Midazolam 1-5 mg i.v. Diazepam 2-10 mg i.v. Lorazepam 2 mg i.v.
Vasodilators:	Nitroglycerine 10 mcg/min by continuous infusion Nitroprusside 0.5-10 mcg/Kg/min by continuous infusion Phentolamine 5-10 mg i.v.

Alpha-beta blockers:	Labetalol 10-20 mg i.v., followed by 2-8 mg/min by infusion
Ca Channel Blockers:	Diltiazem 5-20 mg i.v.
	Verapamil 5-10 mg i.v.

IV.B. Hypotension

Recognition: Drop in blood pressure to below 90/50 mm Hg or subject complaints of dizziness or fatigue associated with drop in blood pressure from baseline.

Treatment: Discontinue cocaine infusion. Maintain subject in supine position. If symptoms and signs continue, give normal saline bolus of 500 cc over 20 minutes, i.v.

IV.C. Change in Heart Rhythm

IV.C.1. Atrial Arrhythmias

Recognition: The arrhythmia most likely to be observed is new onset of supraventricular tachycardia, and may not require treatment, unless of hemodynamic significance.

Treatment: Stop cocaine infusion then administer treatment. First line treatment with sedatives is recommended, followed by Ca^{+2}-channel blockers, in the same doses described above. The use of adenosine in the setting of acute cocaine use has not been examined.

Benzodiazepines:	Midazolam 1-5 mg i.v.
	Diazepam 2-10 mg i.v.
Ca^{+2}-Channel Blockers:	Diltiazem 5-20 mg i.v.
	Verapamil 5-10 mg i.v.

Other tachyarrhythmias (atrial fibrillation, atrial flutter) are unusual except in the presence of preexisting cardiac disease. Treatment along standard guidelines is appropriate.

IV.C.2. Ventricular Arrhythmias

Recognition: Coronary vasoconstriction from cocaine can induce ventricular ectopy, especially in the presence of high circulating levels of catecholamines. Cocaine also can prolong the QT interval, reduce the threshold for ventricular irritability, and cause early after depolarizations that can trigger ventricular arrhythmias (6). Premature ventricular contractions and more serious arrhythmias, such a ventricular bigeminy and ventricular tachycardia, should be considered to be due to ischemia first, and first line treatment should be directed to improve myocardial oxygen supply.

Treatment: Lidocaine has been used safely to treat malignant ventricular arrhythmias due to cocaine. However, Lidocaine decreases the seizure threshold and can increase block through the

normal conduction pathway (7). Other antiarrhythmics that prolong the normal action potential should be avoided: Quinidine, Procainamide, Disopyramide (2). The latest Advanced Cardiac/Cardiopulmonary Life Support (ACLS) guidelines recommend Amiodarone infusion for either stable or unstable ventricular tachycardia, but not for Torsades or in combination with other drugs that prolong the QT interval.

QT prolongation and wide-complex tachycardia (Torsades de Pointes) is safely and effectively treated with i.v. magnesium by infusion (2).

IV.C.2.a. Ventricular Fibrillation

Recognition: Clinical cardiac arrest with ventricular fibrillation on ECG and **absence** of carotid pulse.

Procedure: Stop cocaine infusion then administer treatment as follows:

1. If arrest witnessed, apply a precordial thump then check pulse and ECG rhythm.
2. If no pulse, begin CPR.
3. Defibrillate (unsynchronized) at 200 joules (J) and check pulse and ECG rhythm. If no change, repeat defibrillation at 300 J. Check pulse and rhythm. If still no change, defibrillate at 360 J. Check pulse and rhythm.
4. If above not successful in generating pulse, continue CPR
5. Give Epinephrine 1 mg i.v.. push.
6. Repeat defibrillation at 360 joules. Check pulse and rhythm.
   - **NOTE:** When giving medications, do so in a **drug-shock-drug-shock sequence**. Check pulse and rhythm immediately after defibrillation.
7. Give Amiodarone 300 mg i.v. push. May repeat once in 3-5 minutes at dose of 150 mg i.v.
8. Repeat defibrillation at 360 J. Check pulse and rhythm
9. Draw arterial blood gases.
10. Give Lidocaine 1-1.5 mg/Kg i.v. May repeat in 3-5 minutes. Maximum loading dose 3 mg/kg.

IV.C.2.b. Sustained Ventricular Tachycardia*

Recognition:

1. Ventricular tachycardia on ECG associated **with stable BP > 90/60** = Stable V-tachycardia.
2. Ventricular tachycardia on ECG associated **with a fall in BP < 90/60**, change in mental status, chest pain, or congestive heart failure (CHF) = Unstable V-tachycardia.

Procedure: Stop cocaine infusion then administer treatment as follows:

For Stable Ventricular Tachycardia:

1. Apply oxygen at 100%

2. Give Amiodarone 150 mg i.v. over 10 minutes
3. Apply synchronized cardioversion, start with 50 joules (J). If no response go to 100 J, if still no response go to 200 J. To effectively deliver a synchronized or synchronous electrical current to the myocardium to terminate lethal arrhythmias using R2 Cath-Pads.

For Unstable Ventricular Tachycardia:

Normal QT:
1. Apply oxygen at 100%
2. Give Amiodarone 150 mg i.v. over 10 minutes
3. Apply synchronized cardioversion, start with 50 joules (J). If no response go to 100 J, if still no response go to 200 J. To effectively deliver a synchronized or synchronous electrical current to the myocardium to terminate lethal arrhythmias using R2 Cath-Pads.

Prolonged QT/Torsades:
1. Give Magnesuim sulfate 2-6 mg i.v. over 10-40 minutes or 5-20 mg/min
2. Overdrive pacing

*** NOTE: If patient is pulseless at any time treat as ventricular fibrillation.**

IV.C.2.c. Ventricular Extrasystoles

Recognition: Ventricular extrasystoles, single or multiple, unifocal or multifocal.

Treatment: Discontinue cocaine infusion if frequent or repeated (three or more in 1 minute). If extrasystoles remain frequent or repeated, give Lidocaine 100 mg i.v. followed by infusion of 2 mg/min.

IV.C.3. Bradycardia - Severe

Recognition: Pulse rate and ventricular rate under 40 associated with fall in BP below 90/60, change in mental status, chest pain, or dyspnea.

Procedure: Stop cocaine infusion then administer treatment as follows:

1. Give Atropine 1 mg i.v. push and obtain ECG rhythm strip.
2. Transcutaneous pacing (to be done immediately with severely symptomatic patients)
3. Give Dopamine 5-20 mcg/Kg/min
4. Give Epinephrine 2-10 mg/min
5. Give Isoproterenol 2-10 mcg/min

IV.C.4. Ventricular Asystole

Recognition: Clinical cardiac arrest by ECG in two leads and absence of carotid pulse.

Procedure: Stop cocaine infusion then administer treatment as follows:

1. Begin cardiopulmonary resuscitation (CPR)
    a. Give Epinephrine 1 mg i.v. push.
    b. Give Atropine 1 mg i.v. every 3-5 minutes. Maximum dose 0.04 mg/Kg.
2. Continue resuscitation until effective heart action returns.
3. Draw arterial blood gases.

IV.C.5. Sinus Tachycardia

Recognition: From continuous pulse monitoring, pulse elevated over 160 BPM.

Procedure: Immediately stop cocaine infusion, monitor pulse rate. If patient symptomatic or if rate does not lower below 160 after 1 minute, treat as hypertensive crisis.

IV.D. Chest Pain

Recognition: By complaint.

Procedure: Discontinue cocaine infusion. Note heart rate and blood pressure and review 12 lead ECG for evidence of myocardial ischemia.

1. Administer Oxygen
2. Give sublingual nitroglycerine 0.4 mg
3. Give Aspirin
4. Give beta-blocker (treat with Labetolol if BP is significantly elevated)
5. Give Benzodiazepines (Lorazepam 2 mg i.v. Push)
6. If chest pain persists, give Calcium channel blockers (Verapamil 5 mg i.v. over 3 minutes) and/or Phentolamine 1 mg i.v.

IV.E. Seizures

Recognition: Loss of consciousness associated with bilateral eye deviation, and/or tonic-clonic movements of one or more extremities. Epileptiform seizure activity seen on EEG monitoring is confirmatory, but treatment should not be delayed in order to obtain an EEG.

Procedure: Since benzodiazepines rapidly enter the brain and control seizures, they are most often used as the first line of therapy. Apnea is frequently seen in the post-ictal state, whether the seizure arrests spontaneously or is treated.

1. Stop cocaine infusion.

2. Administer 100% oxygen by facemask and manual-bag inflation device immediately. If the patient does not resume spontaneous control of the airway, or there is evidence of regurgitation, suction and intubate the trachea. Continue manual ventilation with 100% oxygen.
3. Give Diazepam 10-15 mg i.v. at 4 mg/min or Lorazepam 2 mg at 5 min intervals to 10 mg.

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APPENDIX IV: Instructions For Evaluating And Reporting Adverse Events And Serious Adverse Events

A. GENERAL INSTRUCTIONS

1. AEs will be reported as soon as the subject signs the informed consent form.

2. Report the severity of the event following the guidance in section B below.

3. Report the relatedness of the event to the study agent administration according to the guidance in section C.

B. DEFINITIONS – SEVERITY OF EVENTS

Mild: Awareness of symptom, but easily tolerated.

Moderate: Discomfort enough to cause interference with usual activity.

Severe: Incapacitating with inability to work or do usual activity.

C. DEFINITIONS – RELATEDNESS OF EVENTS

The investigator is responsible for defining, in his/her best judgment, the relationship of the AE/SAE to the study drug/placebo. The degree of certainty for which the AE/SAE is attributed to the study drug or alternative causes (e.g. natural history of the underlying disease, concomitant therapies, etc.) should be determined by how well the experience can be understood in terms of one or more of the following:

Exposure: Is there evidence that the subject was actually exposed to the drug/placebo?

Timing of the study drug/placebo: Did the AE/SAE follow in a reasonable temporal sequence from administration of the drug test?

Consistency with study drug profile: Known pharmacology and toxicology of the study drug in animals and man; reaction of similar nature having been previously described with the study drug.

Alternative explanations for the adverse event such as concomitant medications, concurrent illness, non-medicinal therapies, diagnostic tests, procedures or other confounding findings.

Response to discontinuation of the study drug/placebo.

Terms and definitions to be used in assessing the study agent relationship to the AE/SAE are:

Unknown:
Use this category only if the cause of the AE/SAE is not possible to determine.

Definitely Not Related:
The subject did not receive the test drug, the temporal sequence of the AE/SAE onset relative to administration of the test drug is not reasonable, or there is another obvious cause of the AE/SAE.

Remotely Related:
There is evidence of exposure to the test drug or there is another more likely cause of the AE/SAE

Possibly Related:
There is evidence of exposure to the test drug, the temporal sequence of the AE/SAE onset relative to administration of the test drug is reasonable, but the AE/SAE could have been due to another equally likely cause.

Probably Related:
There is evidence of exposure to the test drug, the temporal sequence of the AE/SAE onset relative to administration of the test drug is reasonable, and the AE/SAE is more likely explained by the test drug than by any other cause.

Definitely Related:
There is evidence of exposure to the test drug, the temporal sequence of the AE/SAE onset relative to administration of the test drug is reasonable, the AE/SAE is more likely explained by the test drug than by any other cause, and the AE/SAE shows a pattern consistent with previous knowledge of the test drug or test drug class.

D. SPECIFIC INSTRUCTIONS – LABORATORY/ECG ADVERSE EVENT

A laboratory or ECG AE is any clinically significant worsening in a test variable that occurs during the course of the study, whether or not considered to be study agent related. For each such change, provide the information requested on date of test, severity, likelihood of a relationship to investigational agent, change in investigational agent dosage due to the AE, and treatment required.

All laboratory AEs should be specified as an increased or decreased test result (e.g. “increased glucose”, “decreased potassium”) or as a term that implies an abnormality (e.g., hypercalcemia, azotemia).

E. SERIOUS ADVERSE EVENT AND UNEXPECTED ADVERSE EVENT REPORTING

24 hour Reporting Requirements

Any serious adverse event, including death due to any cause, which occurs to any subject from the time of admission through discharge whether or not related to the study drug/placebo, must be reported ***within 24 hours*** to the NIDA Medical Monitor, the NIDA Project Officer, and the Principal Investigator.

The following information must be provided with the initial report of an SAE or unexpected AE:

Name of person reporting the SAE/unexpected AE
Subject's I.D. number
Name of the principal investigator and institution
Description of the SAE/unexpected AE
Date and time of Onset
Date/time of administration of last dose of study agent/placebo prior to the SAE/unexpected AE
Severity of the SAE/unexpected AE
Investigator's assessment of the relationship of the SAE/unexpected AE to study drug (related, possibly related, probably related, unlikely related, not related)
Any action taken with the study drug, alteration to protocol defined schedule, diagnostics, and treatments secondary to the SAE/unexpected AE.

3-day Supporting Documentation Requirements

Written documentation for all SAEs/unexpected AEs must be received by the NIDA Medical Monitor/Alternate and the IND sponsor within 3 days of reporting the event. Required documents that must be submitted include the following:

- SAE Form
- Concomitant Medication CRF pages
- Adverse Events CRF pages
- Copies of source documents pertinent to the event (lab reports, ECG tracings, medical chart notes, etc.)
- Any other relevant information necessary to facilitate the investigator's judgment regarding the SAE's relatedness to the severity OR by request of the Medical Monitor/Alternate

Follow-Up of All Adverse Events/Serious Adverse Events

All adverse medical events must be followed until they are resolved, or until all attempts to determine the resolution of the AE/SAE are exhausted. This may require an extended inpatient period or a change in status from outpatient to inpatient. All treatments, outcomes and information regarding whether or not the subject was referred to their Primary Care Provider for additional follow-up must be recorded in the source document. All serious and unexpected adverse events occurring 30 days after administration of the last dose of study drug/placebo must be reported.

The investigator is required to provide the Medical Monitor/Alternate and the IND sponsor with all relevant follow-up information necessary to facilitate a thorough understanding of the event and judgment regarding the relationship to the study drug/placebo.

Reporting to the FDA

The IND sponsor, is required to report SAEs to the FDA:

- in 7 days if the SAE is unexpected (or, if expected, unusually serious or rarely seen), life-threatening or lethal, and at least possibly related to the study agent, with a follow-up written report in 8 days;

- in 15 days if the SAE is unexpected (or, if expected, unusually serious or rarely seen), but not immediately life-threatening; and

- in an annual report in all other cases.

APPENDIX V: Procedure for Applying for a Certificate of Confidentiality

The only people who will know the identity of the subjects are members of the research team and, if appropriate the physicians and nurses. No information about the subjects, or provided by the subjects during the research, will be disclosed to others without the subjects' written permission, except:

- if necessary to protect subjects' rights or welfare, or
- if required by law.

When the results of the research are published or discussed in conferences, no information will be included that would reveal subjects' identity. Authorized representatives of the FDA and NIDA study monitors may need to review records of individual subjects. As a result, they may know subjects' names, but they are bound by rules of confidentiality not to reveal their identity to others. The results of this study including laboratory results and clinical information collected during this study will be submitted to the FDA and may be used for research purposes. The results of this study may be published but will not personally identify any subjects. All records will be kept in locked storage locations that will be accessible only to authorized study personnel.

Applying for a Certificate of Confidentiality

A Certificate of Confidentiality helps researchers protect the privacy of subjects in health research projects against compulsory legal demands (e.g., court orders and subpoenas) that seek the names or other identifying characteristics of research subjects. The certificate was developed to protect against the involuntary release of personally identified research information of a sensitive nature sought through any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. This authority was granted under the Comprehensive Drug Abuse Prevention and Control Act of 1970, Public Law No. 91-513, Section 3(a).

Investigators will obtain a certificate to avoid being required to involuntarily disclose personally identifiable research information about individual study subjects. Under this statute:

"The Secretary [of the Department of Health and Human Services] may authorize persons engaged in biomedical, behavioral, clinical, or other research (including research on mental health, and on the use and effect of alcohol and other psychoactive drugs) to protect the privacy of individuals who are the subject of such research by withholding from all persons not connected with the conduct of such research the names or other identifying characteristics of such individuals. Persons so authorized to protect the privacy of such individuals may not be compelled in any Federal, State, or local civil, criminal, administrative, legislative, or other proceedings to identify such individuals" (Public Health Service Act 301 (d), 42 U. S. C. 241 (d), as amended by Public Law No. 100-607, Section 163 (November 4, 1988)).”

Accordingly, this special privacy protection can be granted only to research (i.e., a systematic

investigation, designed to develop or contribute to generalizable knowledge). It is granted only when the research is of a sensitive nature where the protection is judged necessary to achieve the research objectives.

The Investigator will submit the application, as outlined in the Confidentiality Certificate Application Instructions (http://www.nida.nih.gov/Funding/ConfidentialityInstruct.html), along with IRB review documentation and a copy of the informed consent/assent forms to be used in the study. The Principal Investigator must sign the application and submit everything to:

Ms. Jacqueline R. Porter
NIDA Certificate of Confidentiality Coordinator
or
Ms. Sandra Solomon,
Certificate of Confidentiality Assistant

Office of Extramural Affairs
6001 Executive Boulevard, Room 3158, MSC 9547
Bethesda, Maryland 20852-9547
Rockville, MD 20852 (courier or express mail)
TEL: 301-443-2755
FAX: 301-443-0538
E-MAIL: jporter@nida.nih.gov or ssolomo1@nida.nih.gov

Since a certificate is generally issued to a sponsoring research institution, the application and its assurances, must be signed by a faculty member or a senior official. The principal investigator, or their staff, will not represent the issuance of a Certificate to potential participants as an endorsement of the research project by DHHS or use it in a coercive manner for recruitment of subjects. The investigator must use the authority of the Certificate to resist compulsory disclosure of individually identifiable research data.

The study subjects should be informed that a Certificate is in effect, and be given a fair and clear explanation of the protection it affords, including the limitations and exceptions. This information will be included in the informed consent. Please see below some suggested wording:

"We have received a Certificate of Confidentiality from the National Institute on Drug Abuse, which will help us protect your privacy. The Certificate protects against the involuntary release of information about your participation in this study. The researchers involved in this project cannot be forced to disclose your identity or your participation in this study in any legal proceedings at the federal, state, or local level, regardless of whether they are criminal, administrative, or legislative proceedings. However, you or the researcher may choose to voluntarily disclose the protected information under certain circumstances. For example, if you or your guardian requests disclosure of your participation, the researchers will provide research data. The Certificate does not protect against that voluntary disclosure.

Furthermore, federal agencies may review our records under limited circumstances, such as a DHHS request for information for an audit or program evaluation or a Food and Drug Administration request under the Food, Drug and Cosmetics Act."

or

"A Certificate of Confidentiality has been obtained from the Federal Government for this study to help insure your privacy. This Certificate means that the researchers cannot be forced to tell people who are not connected with the study, including courts, about your participation, without your written consent. If we see [learn] something that would immediately endanger you, your child, or others, we may discuss it with you, if possible, or seek help."

Study subjects will be notified that a Certificate has expired if they are recruited to the study after the expiration date of the Certificate and an extension of the Certificate's coverage has not been granted.

If the research scope of a project covered by a Certificate should change substantially, the PI will request an amendment to the Certificate; however, the NIDA Certificate Coordinator may require a new Certificate depending on the extent of the change in scope. An extension of coverage must be requested if the research extends beyond the expiration date of the original Certificate, as research information collected after the expiration of a Certificate is not protected from compelled release.

A Certificate of Confidentiality is a legal defense against a subpoena or court order, and is to be used by the researcher to resist disclosure. The researcher should seek legal counsel from his or her institution if legal action is brought to release personally identifying information protected by a certificate. The Office of General Counsel for DHHS is willing to discuss the regulations with the researcher's attorney.