I. *Precis*

Phentermine and fenfluramine are clinically available appetite suppressants which have been shown in double-blind placebo-controlled studies to facilitate and maintain weight loss, both alone and in combination, for periods of up to 3 years (24,25,28,32). Dr. Hitzig recently reported that daily administration of phentermine (30 mg) combined with fenfluramine (up to 80 mg) (FEN/PHEN) reduced craving for alcohol, facilitated the maintenance of abstinence and substantially decreased self-reported depressive symptoms, often starting with the first dose (12). Since the publication of that paper, Dr. Hitzig has treated about 180 alcoholic patients (with 15% drop-outs) and 50 cocaine addicts (with about 30% drop-outs). Dr. Rothman has also independently treated several alcoholic patients with encouraging results. Dr. Hitzig recently treated several cocaine addicts with this medication combination. Dr. Rothman monitored the responses of these patients for 4 weeks. This open-label pilot study (a copy is attached) demonstrated a significant treatment effect without significant adverse effects (21). These open-label studies strongly suggest that FEN/PHEN may be useful for the pharmacotherapy of cocaine and alcohol addiction. Clearly, double-blind placebo-controlled outpatient efficacy studies are needed to confirm these initial encouraging results.

In the present study we propose to initiate the process of conducting a pilot double-blind trial of FEN/PHEN as a treatment for cocaine addiction. Phase 1 of the study will be a double-blind placebo-controlled inpatient safety study of the interaction of cocaine with FEN/PHEN. This is necessary because patients under treatment for cocaine addiction often relapse and use cocaine. Phase 2 of the study will be a double-blind placebo-controlled outpatient study of the efficacy of FEN/PHEN as a treatment for cocaine addiction.

II. *Objectives*

Primary specific aim 1: to determine the safety of the cocaine-FEN/PHEN interaction in cocaine addicts and to gather important scientific data as to cocaine's mechanism of action in the central nervous system.

Primary specific aim 2: to compare the efficacy of FEN/PHEN with that of an active placebo (caffeine) as a treatment for people who abuse cocaine. Subjects enrolled in this phase will also participate in two neuroendocrine challenge sessions before and after treatment. **The challenge agents will be phentermine or fenfluramine. This will allow us to determine the effect of chronic treatment with fenfluramine combined with phentermine on the neuroendocrine effects of these agents.**

III. *Introduction*

Considerable data support the hypothesis that mesolimbic dopamine (DA) plays a key role in mediating the reinforcing effects of drugs of abuse as well as the rewarding effects of ingestive behaviors (5,13,34). The existence of neuronal mechanisms common to the rewarding effects of alcohol, cocaine and eating is also supported by the finding that selective serotonin (5-HT) reuptake inhibitors and the 5-HT releaser fenfluramine decrease appetite and modestly decrease intake of alcohol (6,11,15).

Hitzig, noting the similarities between obesity and alcoholism, hypothesized that medications that suppress craving for food might also suppress craving for alcohol and cocaine (12).

Dr. Hitzig was aware that the serotonin agonist, fenfluramine, and the dopamine agonist, phentermine, synergistically promote weight loss and control food cravings (23). He was also familiar with the concepts of the dopamine reward hypothesis that considers dopamine deficiency and its associated pains, e.g. hunger, thirst, lust,

craving, etc. as the prime motivation for action, e.g. eating, drinking fluids, and using drugs; all dopamine-elevating activities. The dopamine elevation resulting from these activities or substances relieve pain. When the rate of D2 post-synaptic increase is modest, Hitzig argues, one enjoys relief of pain or what we commonly call satisfaction. When the rate of D2 post-synaptic filling is rapid enough to give one pleasure, that dopamine agonist whether a substance, thought, or behavior, has addictive potential. Furthermore, he was aware that serotonin, increases in concert with dopamine in the aforementioned activities.

Hitzig reported on the successful treatment of 11 alcoholics with fenfluramine (up to 60 mg per day) and phentermine (30 mg per day) (12). Since the publication of that paper, Dr. Hitzig has since treated about 180 alcoholic patients (with 15% drop-outs) and 50 cocaine addicts (with about 30% drop outs) with encouraging results (12A). Dr. Rothman has also independently treated several alcoholic patients with similarly encouraging results.

Dr. Rothman monitored the first six cocaine addicts treated by Dr. Hitzig for 4 weeks. This open-label pilot study demonstrated a significant treatment effect without significant adverse effects (21). This open-label study (copy attached) suggests that FEN/PHEN may be useful for the pharmacotherapy of cocaine.

Studies (unpublished) conducted in collaboration with Dr. John R. Glowa demonstrated that phentermine selectively reduce cocaine self-administration (relative to food) in rhesus monkeys (see Figure 1). These data provide additional support for the hypothesis that phentermine may be useful in the pharmacotherapy of cocaine addiction in humans.

The ability of animal models of cocaine addiction to identify useful medications for treating cocaine addiction in humans is unclear. The testing in humans of a medication which looks very promising in a well accepted animal model of cocaine addiction will provide the means to validate this widely used animal model. A positive (or negative) result will, therefore, be of considerable importance to the medication development process.

In the present study we propose to initiate the process of conducting a pilot double-blind trial of FEN/PHEN as a treatment for cocaine addiction. Phase 1 of the study will be a double-blind placebo-controlled inpatient safety study of the interaction of cocaine with FEN/PHEN. This is necessary because patients under treatment for cocaine addiction often relapse and use cocaine. This phase will also provide important information as to the mechanism of cocaine's effects in the CNS. Phase 2 of the study will be a double-blind placebo-controlled outpatient study of the efficacy of FEN/PHEN as a treatment for cocaine addiction.

IV *Methods*

Subject selection

Statement on recruitment of women and minority subjects

Based on the 1990 NIDA Houeshold Survey on Drug Abuse, the national population of individuals aged 18-34 years old who use cocaine weekly is estimated at 71% male and 29% female. From an ethnic viewpoint, 26% are African American, 29% are Hispanic and 46% are white. Thus, our recruitment targets will be the above quoted percentages.

Recruitment

For the study, up to **150** subjects will be recruited by newspaper and radio advertisements, word-of-mouth, and referrals using generic advertising already approved by the IRB, with the goal of obtaining a total of **90** completed subjects (10 in phase 1 and 80 in phase 2). Subjects will undergo a detailed medical and psychological evaluation on an outpatient basis as specified in the IRP Medical Policy and Procedure Manual prior to being admitted to the IRP Residential Unit. These procedures/items include:

- Comprehensive medical history
- Complete physical exam
- ASI
- SCL-90R
- Shipley
- TB skin test
- EKG
- 3 min rhythm strip
- Chemistry panel
- CBC
- Urinalysis
- Hepatitis B serology
- Urine toxicology

Subject inclusion criteria (phase 1 - cocaine-FEN/PHEN interaction)

- Males or females 21-35 years of age;
- Past use of IV cocaine;
- Use of cocaine by any route at least twice weekly within the last month.
- Physically healthy for their age, with no history of major chronic or debilitating illness, as determined by a complete physical examination, laboratory tests, EKG and 24-hour Holter monitors; **5)**
- Sufficient intelligence and sufficiently literate to understand the consent form, follow instructions, and complete questionnaires;
- Properly motivated, willing to cooperate with the investigators by taking required medications, and willing to participate in all evaluations
- Positive cocaine metabolites in urine on admission screening.

Subject inclusion criteria (phase 2)

- Males or females 21-44 years of age;\
- Who meet at a minimum DSM-IIIR criteria for cocaine abuse and use of cocaine by any route at least 12 times per month;
- Desire to quit using cocaine as judged by the Principal Investigator or his/her designee. **4)**
- physically healthy for their age, with no history of major chronic or debilitating illness, as determined by a complete physical examination, laboratory tests, EKG.; **5)**
- sufficient intelligence and sufficiently literate to understand the consent form, follow instructions, and complete questionnaires; **6)**
- properly motivated, willing to cooperate with the investigators by taking required medications, and willing to participate in all evaluations;
- willing to give written informed consent prior to participation in the study
- Patient must have a significant other
- who does not use cocaine who does not meet the criteria for dependence on any psychoactive drug except for caffeine or nicotine,
- who will be willing to provide independent information on the patient's cocaine consumption and condition and
- Who has a negative intake urine toxicology screen; Subject exclusion criteria.

As described in the IRP Medical Policy and Procedures Manual, subjects with the following findings from their medical intake will not be enrolled in the study:

History

- Recent unexplained weight loss
- Unexplained fevers of extended duration
- Night sweats
- Syncope
- Myocardial infarction
- Chest pain on exertion
- Chest pain on drug use
- Shortness of breath
- Edema, heart failure
- Paroxysmal nocturnal dyspnea
- Orthopnea
- Palpitations with drug use or requiring medical attention
- Adult asthma
- Emphysema
- Hemoptysis
- Seizures
- Psychosis
- Head trauma with greater than 1 min unconsciousness
- Hyperthyroidism

- Hypothyroidism
- Diabetes mellitus

Physical examination:

- Systolic BP > 160 or < 95
- Diastolic BP > 95
- Pulse rate > 105 or < 50 on a consistent basis
- Respiratory rate > 24
- Jugular venous distention
- Carotid bruits
- S3 heart sound
- Point of maximal impulse beyond the anterior axillary line
- Any valvular disease
- Palpable thrill
- Peripheral edema
- Wheezes
- Cyanosis

EKG

- EKG - Wolfe Parkinson White Syndrome
- EKG - myocardial infarction
- EKG - left bundle branch block
- EKG - PR interval < 0.12 or > 0.20 sec
- EKG - QT interval > 0.43 sec
- EKG - PACs > 3/min
- EKG - PVCs > 1/min

(Only if done):

- CXR - pulmonary hypertension
- CXR - cardiac enlargement
- CXR - pulmonary congestion
- CXR - any active pulmonary process

Laboratory studies:

- AST or ALT > 100 IU/ML
- 47. hematocrit - males < 39%
- hematocrit - females < 36%
- WBC's: < 2500 or > 10,500
- Potassium: < 3.5 or > 6
- BUN > 40
- Creatinine > 1.6
- Glucose < 50 or > 150
- Total bilirubin > 2.0
- Calcium < 8.0 or > 12.0
- Urinalysis - protein >=1+
- Urinalysis - glucose >=1+
- Abnormal thyroid function tests: T3, T4, TSH

Psychometric testing.

- Shipley < 18

Other specific exclusionary factors include:

- Current physical dependence on any psychoactive substance except caffeine or nicotine;
- History of seizures, coronary disorder, diabetes;
- severe or uncontrolled psychiatric or medical conditions which, in the judgment of the investigators, would impair the ability of the subject to safely participate in the study;
- Known allergies to caffeine, phentermine, fenfluramine or other sympathomimetic amines;
- Pregnant or lactating women or women who do not practice a medically accepted method of birth control (oral contraceptives, IUD, condom, sterilization). This exclusion is to avoid exposing a fetus to drugs;
- History of serious adverse medical consequences of cocaine use including stroke, seizures, psychosis, and tachyarhythmias;
- Use of any prescription psychoactive medicine during the previous two weeks including MAO inhibitors.
- Hyperthyroidism as judged by a T3, T4 and TSH levels;
- History of exaggerated responses or adverse reactions to over-the-counter sympathomimetic amines such as pseudoephedrine, phenylpropanolamine or ephedrine;
- Motor tics or a family history of Tourette's syndrome;
- History of glaucoma
- Patients who have heard of the FEN/PHEN treatment will be excluded since this knowledge could bias their response to treatment.

HIV testing and separate counseling will be required. A positive test will not be an exclusionary criteria. Subjects will be tested for HIV because retrospective analysis of the data may reveal important correlation's between HIV status and the results.

B. Procedures.

Description of protocol.

The protocol will be conducted in two phases.

Phase 1: Double-blind safety evaluation of the interaction of intravenous (IV) cocaine with FEN/PHEN in cocaine addicts (10 subjects completing).

This will be a double-blind cross-over study of the effects of daily administration of FEN/PHEN on the cardiovascular and subjective effects of cocaine. Ten subjects will be recruited for this phase. Five subjects will be randomly assigned to group 1 (4 days of placebo, 4 day washout, 4 days of FEN/PHEN) and five subjects will be assigned to group 2 (4 days of FEN/PHEN, 4 day washout, 4 days of placebo). Subjects will wear Holter monitors for the entire duration of the study except for when the data are being off-loaded.

As will be described in greater detail below, the cocaine administration sessions will begin at 9 AM. The design will be a dose-escalation paradigm in which each subject receives saline, 1 mg, 10 mg, 25 mg and then 40 mg of IV cocaine delivered over a 1 min period with each administration occurring at least 30 min apart or until vital signs have returned to baseline-line levels.

The basic time-line for this component of the study is as follows:

Day/Session	Drug Administration	Cocaine Challenge			
		Group 1		**Group 2**	
1	MON	PBO		FEN/PHEN	
2	TUES	PBO		FEN/PHEN	1
3	WED	PBO		FEN/PHEN	
4	THUR	PBO		FEN/PHEN	2
5	FRI	PBO	WASH-OUT	PBO	
6	SAT	PBO	WASH-OUT	PBO	
7	SUN	PBO	WASH-OUT	PBO	
8	MON	PBO	WASH-OUT	PBO	
9	TUES	FEN/PHEN		PBO	
10	WED	FEN/PHEN		PBO	3
11	THUR	FEN/PHEN		PBO	
12	FRI	FEN/PHEN		PBO	4
13	SAT	NONE		NONE	
14	SUN	NONE		NONE	

The dosing schedule will as follows:

8 AM dose will be either phentermine-HCl (37.5 mg equivalent to 30 mg of the base) plus 40 mg fenfluramine (prepared from Pondimin tablets) or placebo.

4 PM dose will be 40 mg fenfluramine (prepared from Pondimin tablets) or placebo.

Signal Averaging-EKGs will be run before each cocaine challenge session.

In addition to the cardiovascular end-points, a number of different measures will be taken to determine the effect of the treatment medications on cocaine-induced subjective and endocrine effects (cortisol, prolactin, ACTH, growth hormone).

Time-Line for Cocaine-Challenge Sessions in Phase 1

Subjects will be asked to abstain from caffeine starting at 12 midnight preceding a cocaine infusion session. A licensed nurse will place two heparin locks. One is to be used for administration of cocaine, the other is to be used for withdrawal of blood samples.

- Visual Analog Scale (VAS) - measures drug liking and cocaine craving
- Profile of Mood States (POMS)
- Questionnaire for Drug Related Feelings (QDRF)
- Performance Assessment Battery (PAB)
- Multiple choice procedure (MCP)
- Motor activity (optional)
- VS - vital signs (HR,BP)
- Pupilometry

There will be continuous EKG monitoring (2 leads) for the duration of the study, or until any abnormalities

return to pre-drug baselines.

IV drugs will be infused over 60 seconds.

0700	Heplocks placed.
0730-0815	Light Breakfast. Signal-averaging EKG
0800	Administration of study medication (FEN/PHEN or Placebo).
	2-lead EKG leads placed and Holter monitor placed. VAS, POMS, QDRF, PAB, Pupilometry
-20 min	VS, blood sample #1
-10 min	VS, blood sample #2
09:00	VS, IV Drug (saline)
+1	VAS
+5	VS, VAS
+10	VS, VAS, Pupilometry
+15	VS, blood sample #3
+20	VS, VAS, QDRF, MCP
09:30	VS, IV Drug (cocaine - 1 mg)
+1	VAS
+5	VS, VAS
+10	VS, VAS, Pupilometry
+15	VS, blood sample #4
+20	VS, VAS, QDRF, MCP
10:00	VS, IV Drug (cocaine - 10 mg)
+1	VAS
+5	VS, VAS
+10	VS, VAS, Pupilometry
+15	VS, blood sample #5
+20	VS, VAS, QDRF, MCP
10:30	VS, IV Drug (cocaine - 25 mg)
+1	VAS
+5	VS, VAS
+10	VS, VAS, Pupilometry
+15	VS, blood sample #6
+20	VS, VAS, QDRF, MCP

11:00	VS, IV Drug (cocaine - 40 mg)
+1	VAS
+5	VS, VAS
+10	VS, VAS, Pupilometry
+15	VS, blood sample #7
+20	VS, VAS, QDRF, MCP

There are 7 blood samples. There will be one 5 cc red top tube taken for measurement of hormones. There will be a second 5 cc green top tube taken for measurement of cocaine levels. This will be done to see if FEN/PHEN alters cocaine metabolism. Thus, total volume of blood to be taken will be 10 cc x 7 or less than 70 cc for each session or 280 cc for the entire phase.

The major safety data in phase 1 are the cardiovascular data. The sets of data relevant to a safety assessment include: a) vital signs (Blood pressure, pulse) as they occur during cocaine administration sessions and as collected by the nursing staff on a qshift basis. b) The Holter monitor data and c) the signal averaging EKG data. As suggested by the Protocol Implementation Review Committee (PIRC) in their meeting of 6/19/95, the MRI will review this data, co-investigators who are physicians, the Clinical Director, Scientific Director, and the Branch Chief. As noted under "VI. Credentials and role of each investigator" Dr. Gorelick will take primary responsibility for reviewing the signal averaging EKG data and Dr. Contoreggi will take primary responsibility for reviewing the Holter monitor data. Dr. Rothman will take primary responsibility for reviewing the vital signs data. There will be a meeting where all these data are reviewed. Clinical events that might trigger a determination that it would be unsafe to proceed into phase 2 are specified in "V. Monitoring and criteria for withdrawal of subjects."

Phase 2: Double-blind placebo-controlled evaluation of the efficacy of FEN/PHEN as a treatment for cocaine addiction (80 subjects completing).

This study will be similar in design to ARC-259 that will examine the efficacy of FEN/PHEN for treating alcoholism. Subjects who are medically cleared for the study (see section A) will be scheduled for their first appointment.

Prior to random assignment to treatment groups, all subjects will participate in two neuroendocrine challenge sessions conducted on an outpatient basis at least two days apart (for example Monday and Wednesday). Each subject will receive phentermine (30 mg base, 37.5 mg of the HCl) in one session and fenfluramine (80 mg) in the other. The challenge sessions will then be repeated in the 14th week of the study when all patients will be receiving placebo. The order of the sessions will be counterbalanced.

Rationale for the neuroendocrine challenge sessions

As noted in the section on "risks" it is well established that amphetamines such as fenfluramine and methamphetamine are neurotoxic when administered intravenously in large doses to animals (19). The term neurotoxic refers to a depletion of DA nerve terminals and 5-HT nerve terminals by methamphetamine and fenfluramine, respectively. The clinical significance of this is still not clear. For example, Dr. Ricaurte, an expert in this area, said "although findings in animals are compelling, observations in humans are less clear. In particular, it remains to be determined whether amphetamine analogues damage central monoaminergic neurons in humans and, if they do, whether functional consequences ensue." Since subjects in this treatment study will be taking FEN/PHEN, the study provides the opportunity to probe for the occurrence of such neurotoxicity. We will do this by determining if chronic treatment with FEN/PHEN blunts the neuroendocrine effects of phentermine alone (to probe

the DA nerve terminal) and fenfluramine alone (to probe the 5-HT nerve terminal). This is likely to be a sensitive measure of such neurotoxicity since studies in rats have demonstrated that administration of neurotoxic doses of fenfluramine blunts the subsequent neuroendocrine effects of fenfluramine (Baumann and Rothman, unpublished data) and since human users of the amphetamine congener MDMA, which depletes 5-HT nerves, have a blunted response to the serotonergic agent L-tryptophan (Price et al, Arch. Gen. Psych. 46:20-22, 1989). Plasma prolactin will be end-point for the neuroendocrine sessions).

An additional reason for challenging subjects with phentermine prior to their assignment to treatment groups is that clinical experience indicates that some individuals do not seem to respond to the usual dose of phentermine (30-mg base, 37.5 mg of the HCl). In clinical practice, the treating physician can simply increase the dose to achieve the desired response. In the context of a placebo-controlled clinical trial, this is not possible. Thus it will be important not to enroll patients who are phentermine-unresponsive, since such patients may end up being treatment failures. Our end-point criteria for enrollment in the treatment component of phase 2 will be that the oral dose of phentermine produces at least a 20% increase in the resting heart rate. As noted in the section on Risks, phentermine characteristically produces an increased heart rate, an effect that seems to decrease as the body adjusts to the medication.

The neuroendocrine challenge sessions will also allow us to identify the unusual person who experiences a dysphoric psychological reaction or adverse cardiovascular response to phentermine or fenfluramine. Such a person will be medically discharged from the study.

Procedure for Neuroendocrine challenge sessions.

After being medically cleared for the study, patients will report to the ARC at about 7:00 AM for the first two neuroendocrine challenge session. Although the end-point for determining entry into the study will be the heart rate, we will also take blood samples to obtain novel data on the hormonal effects of phentermine. Even though all patients will receive either phentermine or fenfluramine, the consent form will say that they will receive either placebo, fenfluramine or phentermine. This is to eliminate expectancy effects. The time-line will be as indicated below:

Patients will have a heparin lock inserted into an arm vein and serial samples of blood will be withdrawn to determine the hormonal effects of phentermine. The heart rate and EKG will be monitored for the duration of the session with a 2-lead EKG monitor. The time-line will be as follows:

	Visual Analog Scale (VAS) - measures drug liking **CCS - cocaine craving scale** **Profile of Mood States (POMS)**
0700	**Heparine lock insertion into arm**
0730-0815	**Light Breakfast (juice, toast and cereal)**
0815-0850	**Baseline measures: Vital Signs, VAS, CCS, POMS**
	There will be continuous 2-lead EKG monitoring during the session, including a strip prior to drug administration.
0830	**blood sample #1 for baseline hormones.**

0845	**blood sample #2 for baseline hormones.**
0859	**blood sample #2 for baseline hormones.**
0900	**Oral administration of pretreatment drug [phentermine 30 mg or fenfluramine (80 mg)]**
+30	**VAS, POMS** **blood sample #4**
+60	**VAS, POMS, CCS** **blood sample #5**
+90	**VAS, POMS** **blood sample #6**
+120	**VAS, POMS, CCS** **blood sample #7**
+150	**VAS, POMS** **Blood sample #8**
+180	**VAS, POMS, CCS** **Blood sample #9**
+210	**VAS, POMS** **Blood sample #10**
+240	**VAS, POMS, CCS** **Blood sample #11**
+270	**VAS, POMS** **Blood sample #12**
+300	**VAS, POMS, CCS** **Blood sample #13**
+330	**VAS, POMS** **Blood sample #14**
+360	**VAS, POMS, CCS** **Blood sample #15**

Vital signs q 15 min after 0900 (BP, pulse, temperature, respiration).

Each blood sample will be 2.5 cc for a total of 37.5 cc per session. For the four challenge sessions the total will be 150 cc.

After completing the first two neuroendocrine sessions, the MRI will break that person's blind and medically discharge patients who do not experience a phentermine-induced increase in heart rate of at least 20% over baseline. The other patients will be randomly assigned to one of two groups. Group 1 will receive an active-placebo (caffeine) and Group 2 will receive FEN/PHEN for the first 12 weeks of the study. It is important to have an "active" placebo since phentermine is a mild stimulant that characteristically produces insomnia in the initial phase of treatment. Thus, many patients will be able to determine that they are taking FEN/PHEN if an active placebo such as caffeine is not included. Patients will be titrated off of medication over the 13th and 14th week of the study by going to an every other day administration for three doses followed by placebo administration. Patients will be blinded to the titration procedure. Patients will be randomly assigned to the groups, which will be matched for age. We anticipate achieving statistical power with an n=40 completers in each group (see below) because we anticipate a large treatment effect with the FEN/PHEN, but not the active-placebo group. Patients will be asked to take two pills per day. In clinical practice, the physician adjusts medication doses so as to minimize side effects while maintaining therapeutic effectiveness. Because individuals differ in their responses to medications, the treating physician in this study will be permitted to provide the patients with either "high" dose (red) or "low" dose (blue) capsules. The high dose FEN/PHEN capsules will contain phentermine-HCl 37.5 mg combined with 40 mg fenfluramine for the AM dose and fenfluramine 40 mg for the PM dose. The low dose FEN/PHEN capsules will contain phentermine-HCl 37.5 mg combined with 20 mg fenfluramine for the AM dose and fenfluramine 20 mg for the PM dose. The "high dose" placebo pills will consist of 100 mg caffeine for the AM dose, and 40 mg caffeine for the PM dose. The "low dose" caffeine pills will consist of 50 mg caffeine for the AM dose, and 20 mg caffeine for the PM dose. Since clinical experience has shown that fenfluramine can be used to counteract the insomniac effects of phentermine and to potentiate its anti-craving effects, all patients will be started out on high dose capsules. They can be switched to low dose capsules at the discretion of the treating physician and the consent of the patient if adverse side effects occur.

All patients must have a "significant other" who will provide independent verification of the patients' drug use and who will administer the medications to the patients. The significant other will be a non-drug user. The significant other will be expected to attend all visits to the IRP with the patient. Patients will also be asked to wear skin patches for subsequent analysis of cocaine metabolites. This provides an alternative means to monitor cocaine use. Note that the skin patch method is in the experimental stage and should not be considered a valid reliable outcome measure.

The first appointment after the phentermine-challenge study will be longer than most because several questionnaires must be completed. These are:

- Diagnostic Interview Schedule (DIS, for arriving at more precise psychiatric diagnose than determined the initial recruitment.
- Beck Depression Inventory
- Personality inventory (IVE and PDQ-R)
- Profile of mood states (POMS)
- SCL-90R
- Cocaine craving index
- Description of the pattern of cocaine use.
- "Utah" questionnaire for childhood attention deficit disorder.

At the first visit, patients will also be given a paper-based SCL-90R and Beck to fill out on the fourth day of medication to report on the previous 24 hours. They will also be observed for at least two hours after taking their

first dose of medication. On the third hour after taking their first dose of medication, subjects will fill out an SCL-90R and a craving index. There will also be an observer assessment of craving and mood before and 3 hr after taking medication. This is to evaluate the clinical observations of a rapid antidepressant effect of FEN/PHEN. Patients will also have a skin patch applied.

For subsequent visits, patients will come to the IRP at weekly intervals for assessments and dispensing of the medication. The following procedures will be carried out at each weekly meeting (including the first):

- Vital signs (BP, pulse, respiration rate and temperature).
- Assessment for jugular venous distension and edema to rule
- out pulmonary hypertension.
- Urine sample for a standard toxicology screen.
- Report of drug usage - patient and significant other.
- Administration of SCL-90R, Beck, Craving Index, POMS
- Global function assessment by interviewer and significant other.
- Weight.
- Blood sample for drug levels and prolactin levels (8 cc).
- Collection of skin patches.

The significant other will also be asked to provide a urine sample for toxicology on the weekly visits.

The following procedures will be carried out twice a month (visits 2,4,6,8,10):

1) CBC
2) Electrolytes, blood Urea Nitrogen (BUN), Serum Creatinine glucose, and liver function tests.
3) 12-lead Signal Averaging EKG.
4) Urine pregnancy test.

At the end of the study, patients will be asked what medication they think they received the placebo or FEN/PHEN.

Determination of medication efficacy is critically dependent on the outcome measures used to measure treatment response. Urine toxicological analysis, although the "gold standard" of the field, can be insensitive to large decreases in cocaine use. To maximize the chances of detecting a true treatment effect, we will enroll only those patients who are motivated to stop using cocaine, as determined by the PI or MRI, and who use cocaine at least 12 days in a month. We will also have the significant other administer the capsules to the subject, so that compliance can be separately determined. The main endpoints of the study will be pattern and quantity of cocaine consumption as determined by self- and significant other-reports, the level of cocaine metabolites in the urine, the level of cocaine metabolites in special "skin patches" which patients will wear on a 24 hr basis, the patients level of functioning as determined by the patient, the treating physician and the significant other, and the patient's mood as determined by administration of the SCL-90R and the Beck Depression Inventory.

This study will not be conducted under the aegis of the IRP Archway Clinic because that facility is already filled to capacity with other high priority clinical research studies. Moreover, since we hope to recruit patients similar to those successfully treated by Dr. Hitzig, i.e. generally white-collar and blue-collar people with a serious cocaine problem who at a minimum meet the DSM-IIIR criteria for cocaine abuse, we will need to see patients in the evenings after the Archway Clinic is closed. Thus, we will not be able to provide patients with the usual psychosocial treatment (i.e. counseling). Although formal counseling for drug addiction is a well-accepted and appropriate treatment modality, we have found in private practice that many patients actually prefer not to

participate in formal counseling. Many of these patients have already been through one or more traditional treatment programs without much benefit, and choose not to enroll in either counseling or traditional 12-step programs. In addition, it is important to note that the patients we propose to enroll are problem cocaine users who want to decrease their use of cocaine and who do not necessarily meet the DSM-IIIR criteria for cocaine dependence. These patients are not the type who are generally enrolled in traditional 12-step programs. Thus, we will offer patients a minimal intervention treatment program. In addition to pharmacotherapy, all patients will be referred to and encouraged to attend their local Narcotics Anonymous group. During their weekly visits to the IRP, all patients will also be encouraged to stop using cocaine. Patients who desire other treatment interventions will not be enrolled in this study and will be referred to appropriate local drug treatment programs. Patients who are already enrolled in counseling will not be excluded.

Patients who experience a pronounced positive treatment effect may want to continue their treatment after the study is over. The IRP does not offer continuing outpatient care outside of the context of treatment studies. Thus, the Principal Investigator will refer such patients to community treatment programs if he deems it to be appropriate and if the patients desire it. Under no circumstances will these patients be referred to any of the investigators of this protocol.

A CBC and SMA-18 and 12-lead signal averaging EKG will be repeated before the subject is discharged. Patients will be asked to return to the IRP for a follow-up appointment 3, 6 and 12 months after discharge from the study.

C. Drug Issues.

Drugs to be Used in This Study

Name	Dose	Route	Total Daily Dose
Phentermine-HCl	37.5 mg PO am	oral	37.5 mg
Fenfluramine	20 mg or 40 mg PO bid	oral	40 to 80 mg
Caffeine	100 am/40 pm	oral	140 mg or 70 mg
(active placebo)	50 am/20 pm dose in mg		
Cocaine	0 to 40 mg	IV (over 60 second)	76 mg

The highest dose of cocaine used (for a 70 kg person) is 0.57 mg/kg. The infusion rate is 40 mg/60 sec or 0.67 mg/sec. Thus, both the dose and infusion duration are within IRP guidelines.

Phentermine and fenfluramine are on the market and approved for use in humans. The doses we will use are within the range approved for human use by the FDA. The risks of the medications are described in more detail below.

Cocaine is an investigational drug which has been used safely in many clinical research studies in the US.

Caffeine occurs in coffee, tea, soft drinks and can be purchased over-the-counter across the US.

D. Dependent variables.

The major end-points of phase 1 of the study are:

1) Cardiovascular data obtained from Holter Monitors.
2) Psychological status as indicated by scores on the SCL- 90R, Beck.
3) Reported cocaine craving.
4) Subjective effects of cocaine.

The major end-points of phase 2 of the study are:

1) Pattern and quantity of cocaine consumption as determined by self- and other-reports, cocaine metabolites in the urine and the skin patch.
2) Level of functioning as determined by a global clinical assessment.
3) Retention in treatment.
4) Craving for cocaine.
5) Neuroendocrine results (prolactin levels).

Other end-points:

1) Psychological status as indicated by scores on the SCL- 90R and Beck.
2) Drug levels in the blood.
3) Compliance as reported by the significant other.

E. *Data storage and analysis*

All questionnaires are run on a computer and the data are stored automatically. Any paper and pencil questionnaires will have the person identified only by their IRP-number and will be stored in a locked file cabinet. As each subject leaves the study, all of the data pertaining to that subject are collected on a floppy disk and this and a backup are stored in a locked file cabinet.

The basic statistical approach will be to perform an ANOVA with repeated measures using the dependent variables noted above. The data will also be carefully analyzed from a qualitative point of view to see if any statistically significant changes make sense.

The following power calculations were determine according to a two-sample proportion test. The table below quantifies the number of patients needed in each group to detect a difference between the groups at the p=.05 level (power=0.8), with the end-point being retention in treatment.

% RETENTION IN TREATMENT		**N per group**
Group A	Group B	(2-TAILED T-TEST)
Active Placebo	FEN/PHEN	
60	**90**	**38**
60	**85**	**57**
50	**90**	**25**
50	**85**	**33**
50	**80**	**45**

This calculation indicates that there will have to be a fairly large difference between the responses of the active placebo and FEN/PHEN groups. **We anticipate that we will be able to detect a reasonable treatment effect with 40 subjects per group.**

V. *Monitoring and criteria for withdrawal of subjects*

All subjects are free to withdraw from the study at any time. Subjects who do not comply with the protocol or who develop physical or psychiatric problems that, in the opinion of the MRI or PI, present a significant risk to the patient will be discharged from the study.

Phase 1

In phase 1, the following stop-points will be used after administration of FEN/PHEN or cocaine. That is, the subject will be medically discharged if:

- Patient reports acute chest pain or shortness of breath
- EKG or Holter monitor includes atrial fibrillation, ventricular tachycardia, or any other clinically significant cardiac arrhythmia or signs of cardiac ischemia
- Ectopic beats greater than the baseline rate occur over the duration of the monitoring period.
- Systolic BP > 200 or < 100. Diastolic BP < 60 or >100 mm Hg
- Heart rate < 50 or greater than 85% of the maximal rate as defined by the American Heart Association for the age of the subject (220-age) (or more current IRP policy)
- Mental status changes that in the clinical judgment of the PI or medical officer is of sufficient magnitude may be dangerous to the subject
- Seizure
- Any other drug response which, in the opinion of the MRI, is an unacceptable risk

Policy for administration of IV cocaine:

1) The dose of cocaine must not exceed 0.75 mg/kg and the infusion rate may not exceed 1.0 mg/sec.
2) Subject will not be administered the first dose of cocaine if heart rate > 105 beats per minute or the BP is > 140/90.

In repeat dosing paradigms, where a subsequent dose of cocaine will be administered within 30 min of a previous dose,

1) No more cocaine can be administered if any dose of cocaine increases the heart rate to greater than 85% of the maximal rate as defined by the American Heart Association for the age of the subject (220-age) (or more current IRP policy).
3) Subsequent cocaine administration must be delayed if the heart rate > 120 beats/min or if the BP > 160/95.
4) Subject reports acute chest pain or shortness of breath.
5) EKG or Holter monitoring shows atrial fibrillation, ventricular tachycardia, or any other clinically significant cardiac arrhythmia or signs of cardiac ischemia.

6) Systolic BP > 200 or < 100. Diastolic BP < 60 or >100 mm Hg (or more current IRP policy).
8) Mental status changes which in the clinical judgment of the PI or medical officer is of sufficient magnitude to represent a danger to the subject.
9) Seizure.

Phase 2

In phase 2 of the study, all patients will be checked weekly for weight, vital signs, jugular venous distension, edema and urine toxicology and side effects. Medication compliance is monitored by the significant other. Blood samples for electrolytes, BUN, creatinine, glucose and liver function and pregnancy tests will be drawn every other week, starting with the second visit. Patients will have a 12-Lead signal-averaging EKG done once per month (visits 4, 8, 12 and 14). Dispensing the medication will be temporarily suspended (i.e. held): **1)** if the patient appears to be under the influence of alcohol or other drugs, if the patient's behavior towards staff, other patients or clinical property is inappropriate; **2)** if at any time the MRI or PI feels it is in the patient's best interest to hold the study medication, or **3)** if side effects occur which require evaluation by the MRI.

Patients will be discharged from phase 2 of the study if the following clinical parameters are observed during clinic visits:

1) Patient reports acute chest pain or shortness of breath.
2) Systolic BP > 200 or < 100. Diastolic BP < 60 or >110 mm Hg.
3) Heart rate < 50 or > 120.
4) Mental status changes which in the clinical judgment of the PI or medical officer is of sufficient magnitude to represent a danger to the subject.

1) Any drug response that the MRI considers worrisome.
2) Jugular venous distension or peripheral edema that the MRI considers excessive

Patients will also be medically discharged if the WBC count drops by greater than 15%, if there is a four-fold increase in liver enzyme levels, or if the urine pregnancy test is positive. Administration of medication may be temporarily suspended pending a repeat determination. If the abnormal finding is not observed in the second sample, the patient will not be discharged.

Phases 1 and 2

All subjects will be asked to return to the IRP for medical and psychological follow-up assessments 3, 6 and 12 months after discharge from the study.

IRP physicians are available at all times for consultation and treatment for any medical or psychological problems that might arise.

VI. Credentials and role of each investigator.

Richard B. Rothman M.D., Ph.D. Dr. Rothman is the principal investigator responsible for the overall coordination of the study including protocol preparation, staff supervision, consenting subjects, maintaining data files, data analysis, presentations and publication of the results. Dr. Rothman will be the first author on papers/abstracts resulting from this work (unless otherwise negotiated) and will also function as the MRI of the

study.

Jean L. Cadet M.D. Dr. Cadet will be involved in protocol preparation, consenting subjects, data analysis, presentations and publication of the study. He will provide back-up medical coverage to Dr. Rothman.

David A. Gorelick M.D., Ph.D. Dr. Gorelick will be involved in protocol preparation, consenting subjects, data analysis, presentations and publication of the study. He will provide back-up medical coverage to Dr. Rothman. Dr. Gorelick will take first-author responsibility for the data obtained from thyroid function tests and the signal-averaging EKGs.

Carlo Contoreggi M.D. Dr. Contoreggi will be involved in protocol preparation, consenting subjects, data analysis, presentations and publication of the study. He will provide back-up medical coverage to Dr. Rothman. He will take first-author responsibility for the data obtained from the Holter Monitors.

Charles R. Schuster Ph.D. Dr. Schuster will be involved in protocol preparation, consenting subjects, data analysis, presentations and publication of the study.

Jack E. Henningfield Ph.D. Dr. Henningfield will be involved in protocol preparation, consenting subjects, data analysis, presentations and publication of the study.

VII. Risk/Benefit Evaluation

A. Risks.

Fenfluramine is a commonly prescribed generally well tolerated anorectic medication. The usual dose ranges from 60 mg to 120 mg per day. Its neurochemical mechanism of action is the release of serotonin. Steady state plasma levels are reached within 3 to 4 days. Fenfluramine is contraindicated in persons who have received an MAO inhibitor within the preceding two weeks. Unlike amphetamines, fenfluramine is a CNS depressant. The most commonly observed side effects are drowsiness, diarrhea and dry mouth.

Other less frequent side effects reported in the PDR include: dizziness, confusion, incoordination, headache, elevated or depressed mood, anxiety, nervousness, tension, insomnia, weakness or fatigue, increased or decreased libido, impotency, anorgasmia, agitation, dysarthria, constipation, abdominal pain, nausea, sweating, chills, blurred vision, dysuria, change in urinary frequency, palpitation, hypotension, hypertension, fainting, pulmonary hypertension, itching, rash, urticaria, a burning sensation of the skin, eye irritation, myalgia, fever, chest pain, bad taste in the mouth. There are apparently some reports of fenfluramine abuse (80 to 400 mg). However, fenfluramine is not self-administered by animals (9), is not a psychomotor stimulant (8), and humans do not like taking it (14). Thus, fenfluramine has a low potential for addiction, as reflected by its schedule IV status (see below).

Phentermine hydrochloride is also a widely prescribed and well-tolerated sympathomimetic anorectic agent. The usual clinical dose is 30-mg PO in the morning. Contraindications for treatment with phentermine include advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, allergies or a history of idiosyncratic reactions to sympathomimetic amines and glaucoma.

Subjects with these characteristics will not be enrolled. The usual side effects observed with phentermine may include tachycardia, palpitations, increased blood pressure, over-stimulation, restlessness, dizziness, insomnia, euphoria, dysphoria, tremor, headache, psychotic reactions (rarely), dryness of mouth, unpleasant taste in the mouth, diarrhea, constipation, rashes, changes in libido, and impotence. Phentermine also has a low level of abuse liability. Any one individual is likely to experience only a few readily reversible side effects that tend to diminish over time as the body adjusts to the medication. A psychotic reaction, which occurs rarely, is readily treated with any of a number of antipsychotic agents.

Dr. Hitzig has observed that a few patients develop a hypertensive reaction to over-the-counter cold preparations such as pseudoephedrine. Also, Dr. Hitzig asks patients to abstain from caffeine for the first 3 days of medication with FEN/PHEN so as to minimize over-stimulation. Thus, we will warn patients in phase 2 to consult with the IRP physician before taking over-the-counter cold preparations and to abstain from caffeine for the first 3 days. Subjects in phase 1 will remain caffeine-free during the duration of the study.

The use of phentermine and fenfluramine in a substance abuse treatment program deserves comment in light of the fact that the sections on these medicines in the **Physicians Desk Reference** states that this is contraindicated (18). Phentermine is a weak amphetamine and a schedule 4 controlled substance. Preclinical research data provide evidence phentermine releases DA and has may have a potential for abuse. For example, phentermine is self-administered by baboons (10). However, studies which assessed the reinforcing efficacy of a closely related drug, chlorphentermine, found it to be considerably less reinforcing than cocaine (9) and not reinforcing at all in rhesus monkeys (4). In humans, chlorphentermine does not have an amphetamine-like profile (7). There has been an isolated report of phentermine abuse (22). Clinical experience with phentermine has demonstrated scant evidence of abuse. For example, Weintraub reported no evidence of phentermine abuse in his elegant double-blind controlled studies (23). Animals do not self-administer fenfluramine (10) and has a non-amphetamine-like profile in man (8,14). The investigators believe, therefore, that there is insufficient data to contraindicate the use of either fenfluramine or phentermine in the treatment of drug abuse.

Weintraub and associates have published extensively on the use of phentermine and fenfluramine for the long-term treatment of obesity (23-33). They have treated patients with 30 mg Phentermine in combination with up to 60 mg fenfluramine for up to three years. They did not observe any significant increase in blood pressure or pulse. The most common side effects were dry mouth. Less common side effects were sleep disturbances, fatigue, vivid dreams, and metallic taste. Minor GI complaints were common during the early phases of treatment. In the first phase of the study, 5 of 62 patients reported irregular or fast heart rate or palpitations. These were transient and reversible. No palpitations were observed in the second phase of the study. Treatment with FEN/PHEN had no significant effect on hematological parameters (CBC, WBC, platelets), urinalysis, serum electrolytes, BUN, Creatinine, liver enzymes. EKGs were normal. There was no evidence of drug abuse, such as patients requesting additional drug. Thus, the clinical data reviewed above indicate that this drug combination, which had been administered to people for periods of up to three years, can be safely administered to IRP patients for 12 weeks. In addition, Dr. Hitzig has treated over 100 alcoholics with FEN/PHEN without clinically significant side effects.

Although FEN/PHEN has an established safety record in patients being treated for obesity, there exists only the experience of Dr. Hitzig as a guide to the safety of FEN/PHEN in cocaine addicts. Several published studies (1,2,16,17) suggest that cocaine addicts can suffer from clinically evident cardiac abnormalities. To minimize these risks, we will enroll only subjects who have clinically normal hearts. As a further precaution, we propose to conduct phase 1 before moving onto phase 2. Thus, we will make sure that FEN/PHEN does not produce any "silent" arrhythmias or ischemia in otherwise healthy cocaine addicts.

There are little published data on the interaction of cocaine with FEN/PHEN from the safety point of view. As discussed earlier, several patients treated by Dr. Hitzig for cocaine addiction were independently followed by Dr. Rothman (21). Two of these patients used crack cocaine while on FEN/PHEN. Both patients reported a diminished

euphoric effect and a diminished effect of cocaine on their heart rate. Dr. Hitzig also has treated more than 20 other cocaine addicts who have not come forward and complained to Dr. Hitzig about any adverse interactions with cocaine. Dr. Glowa (see Figure 1) who conducted studies on the effect of IV FEN/PHEN (doses up to 3 mg/kg administered IV over 30 min) on cocaine self-administration in monkeys has not observed any gross behavioral abnormalities in the eight monkeys used in his experiments. For a 70-kg human, these doses would be 210 mg IV, which is considerable higher than the 30 mg of phentermine and 80 mg of fenfluramine to be administered orally to humans in this study. In addition, Dr. Elmer, who has injected FEN/PHEN to greater than 100 mice also did not observe any gross behavioral or toxic effects except at very high doses (see attached letter).

Although we do not anticipate that the combination of cocaine and FEN/PHEN will result in adverse events, this issue must be addressed before proceeding into clinical trial portion of the study (phase 2) since patients under treatment for cocaine addiction will relapse and use cocaine. Phase 1 of the study addresses these safety concerns and at the same time will provide important data as to the effect of FEN/PHEN on the subjective effects of cocaine. The doses of cocaine and the infusion rate we propose to use are within IRP guidelines.

Some patients will also drink EtOH despite being warned not to. As far as we know, the interaction of EtOH with orally administered FEN/PHEN has not been explicitly studied in either animals or humans from the safety point of view. However, the PDR does not mention any specific warning about this except for the usual warning of not mixing EtOH with centrally acting drugs. Clinical experience has demonstrated that people under treatment with FEN/PHEN who relapse and drink EtOH have not come forward and complained to their treating physicians about any adverse interactions. As mentioned above, Weintraub administered FEN/PHEN to a population of obese but otherwise normal individuals many of whom would be expected to be social drinkers. He did not note any adverse interactions between EtOH and FEN/PHEN.

It is well established that amphetamines such as fenfluramine and methamphetamine are neurotoxic when administered intravenously in large doses to animals (19). **The term neurotoxic refers to a depletion of DA nerve terminals and 5-HT nerve terminals by methamphetamine and fenfluramine, respectively.** The clinical significance of this is still not clear. Dr. Ricaurte has said, "although findings in animals are compelling, observations in humans are less clear. In particular, it remains to be determined whether amphetamine analogues damage central monoaminergic neurons in humans and, if they do, whether functional consequences ensue." Studies in which D-fenfluramine (the active enantiomer of fenfluramine) was administered to obese rats via osmotic minipumps, which deliver drug on a continuous basis, resulted in weight loss without neurotoxicity (3). This study more closely mimics the human oral dosing regimen than the intravenous administration studies that are typically used in animals to produce neurotoxicity. Finally, it should be noted that the FDA is aware of these findings and has not withdrawn fenfluramine from the market. Moreover, D-fenfluramine, the active enantiomer of fenfluramine, is being considered for approval for use in humans by the FDA as anorectic despite clear indications that it also is neurotoxic under certain circumstances (20). Finally, it should be emphasized that fenfluramine has been used in humans for decades with good safety margin and that the dose we propose to use here is within the dose-range approved for use in humans by the FDA. Despite our confidence about the safety of using fenfluramine at the usual clinical doses, a study designed to detect neurotoxicity (the neuroendocrine challenge sessions) has been incorporated into phase 2 of this protocol.

Side effects of cocaine include bradycardia, hypertension, hypotension, tachyarrhythmia, myocardial infarction, tremulousness, seizures, stroke, psychosis and death. To minimize these risks, we will proceed according to a gradual dose run-up procedure and only subjects who have not experienced serious adverse medical consequences of their cocaine use will be used. All subjects must have a healthy cardiovascular system, as judged by physical exam, medical history, EKG and 24 hour Holter monitoring. A licensed physician certified in ACLS in the presence of a licensed nurse will give all IV injections. A crash cart will be available near by. Should it become necessary, subjects can be sent to the Johns Hopkins Bayview Medical Center (JHB) emergency room for

additional treatment.

The investigators and medical staff will be prepared to address psychological or medical issues that may arise during the study. An IRP physician is available 24 hours a day for consultation with IRP health personnel. IRP health personnel will be available 24 hours a day in the event of a medical emergency. If immediate medical assessment or intervention is required, then the subject will be referred to the appropriate medical facility.

Caffeine is both sold over-the-counter in drug stores and is present in coffee and soft drinks. The maximum total daily dose we propose to administer (140 mg) is well within the range commonly consumed by people (a cop of coffee has about 100 mg caffeine) and does not pose significant risks.

A small amount of pain and local bruising is expected to result from venipuncture for blood sampling. There is, in addition, a very small chance of an infection. The amount of blood to be drawn (280 cc for phase 1 and 420 cc for phase 2) does not represent a significant risk. Placement of EKG leads may irritate the skin.

B. Benefits.

Phase 1

All subjects recruited for phase 1 benefit from the free physical and psychological examination that is part of the intake procedure. In the event a medical disorder is discovered by the intake procedure, patients are referred to JHB Medical Center for additional medical treatment. Subjects receive limited medical care for acute benign conditions. Otherwise, subjects are referred to JHBMC or their private physician for additional diagnostic tests or necessary treatment. Subjects also benefit from free room and board and a variety of educational and recreational activities. A subject desiring treatment for his/her substance abuse problem is offered free treatment via a referral to the IRP's Archway Clinic. Appropriate referrals are also given to subjects who require assistance with housing and other social service needs.

Phase 2

All patients recruited for this study benefit from the free physical and psychological examination that is part of the intake procedure. In the event a medical disorder is discovered by the intake procedure, patients are referred to JHB Medical Center or their private physician for additional medical treatment.

A distinct benefit of this study is the possibility that patients may experience a therapeutic effect. FEN/PHEN has been reported to help people decrease their intake of drugs and markedly improve psychic well-being. Patients who experience a positive treatment effect associated with medication may want to continue their treatment after the study is over. The IRP does not offer continuing outpatient care outside of the context of treatment studies. Thus, the Principal Investigator will refer such patients for continuing treatment in the community if he deems it to be appropriate and if the patients desire it.

All patients will be informed of the results of the study at its end, and will be referred to a private physician or other treatment facility for continued treatment should the medication be found to be effective.

IX. Compensation

Phase 1

Subjects will be compensated $50.00 on admission to this 7 to 10 day study whether they complete the

study or not. They will be paid $20.00 for each day spent on the unit. For successful completion of the study, they will receive a bonus of $50.00 for each week of the study. Subjects who leave the study against medical advice, will keep 50% of money accumulated up to that time. Subjects who are medically discharged will receive a prorated amount of their completion bonus. If follow-up visits are scheduled, subjects will receive $ 40, $ 60 $ 80 for the 3-month, 6-month and 12-month follow-up visits, respectively, to compensate them for their inconvenience.

Phase 2

In phase 2, patients will not receive any direct compensation for participating in the study. After the study, patients will receive $50, $100 and $200 for the 3-month, 6-month and 12-month follow-up appointments, respectively. The significant other will be compensated $20 per visit to the ARC. The significant other will also receive $50, $100 and $200 for the 3-month, 6-month and 12-month follow-up appointments, respectively. Significant others will receive a total of $630 and patients will receive a total of $350.

X. Consent and confidentiality issues

The Principal Investigator or his/her designee in the presence of a witness will interview subjects in order to obtain informed consent during an interview with the subject. The drug-use history of the subject will be gathered to make sure that it is consistent with that required by the protocol. The entire consent form will be read to the subject, who is instructed to read along and to ask any questions at any time. The subject indicates informed consent by signing the consent form. Prior to participating in the study, subjects must answer 10 true or false questions that test their understanding of the risks and benefits of the study. They can not enroll in the study unless they answer at least seven questions correctly.

All subject records generated by IRP staff will be accessible only to authorized NIDA/IRP staff and will be kept in locked files. Code number will identify all data forms. The key linking code numbers with subjects' names will be kept by the principal investigator in a locked file. The IRP will not release subject information to outside agencies without subjects' explicit consent to the extent legally possible. However, in the event of a medical emergency, pertinent medical information will be provided to the attending physicians. A confidentiality certificate will be obtained from the Federal Government. Authorized representatives of the FDA may review subjects records.

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