Extending long-term outcomes through an adaptive aftercare intervention

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Protocol

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Reinforcement interventions have pronounced effects on reducing cocaine use. We developed and evaluated a low-cost reinforcement intervention, systematically moving it through the Stages of development to dissemination and broad clinical implementation. In an ongoing project, reinforcement interventions are yielding benefits when reinforcers are provided at treatment initiation and for longer durations. However, less than half of patients remain engaged for 12 weeks with traditional reinforcement interventions, which require frequent attendance for monitoring and reinforcing abstinence. Interventions that extend into aftercare and that are acceptable to and efficacious in preventing long-term relapse are critically needed.

Reinforcement interventions are efficacious during periods they are in effect, and pilot data show that variable interval (VI) reinforcement schedules, once behavior change occurs, hold potential for maintaining gains when administered infrequently. Assessing methods to extend benefits of these interventions is of paramount scientific and clinical concern. This study will evaluate a novel approach in which reinforcement frequency varies by patient performance. In this intervention, reinforcement will be available for 24 weeks, on a progressive VI schedule, that adapts according to patient status. Patients who maintain abstinence earn maximum reinforcers as infrequently as every three weeks on average, while frequency of monitoring and reinforcing abstinence will increase in those who relapse until abstinence is re-instated.

To test efficacy, 280 patients with cocaine use disorder will be randomly assigned to: standard care (SC), SC+traditional twice weekly reinforcement, or SC+adaptive VI reinforcement. Evaluations will be completed at baseline and throughout 18 months to assess objective and self-reported indices of drug use, psychosocial problems, and HIV risk behaviors. Primary hypotheses are (1) the adaptive VI reinforcement intervention will improve outcomes relative to standard care during the treatment period and throughout follow-up, and (2) the adaptive VI reinforcement intervention will improve outcomes relative to the traditional reinforcement system. This study will also evaluate the roles of cognitive control and treatment outcome. Patients with better cognitive control are expected to maintain longer durations of abstinence across conditions. If these measures differentially relate to outcomes across treatments, such results suggest the potential of pairing reinforcement interventions to individuals most likely to benefit from them; they may also indicate possible markers of response in a treatment-specific manner. If cognitive indices mediate treatment response, future studies can refine interventions to improve cognitive processes and long-term outcomes.

Specific aims

Designed and tested using the NIH Stage Model of psychotherapy development (Onken et al., in press), reinforcement interventions hold great potential to improve drug abuse treatment outcomes. Community clinics are increasingly applying these interventions, but methods to maintain their benefits long-term are needed. Extending **the effects of reinforcement interventions would be a major step forward in increasing the efficacy and acceptability of this approach**. Traditional approaches toward reinforcement, requiring frequent clinic attendance, limit acceptability among both patients and providers, especially when applied over long durations. We have pilot data suggesting the efficacy of a gradually increasing variable interval (VI) reinforcement schedule in maintaining behavior gains. This study will evaluate this approach for improving short- and long-term drug use outcomes. It will also address potential cognitive mechanisms of action.

In total, 280 patients initiating treatment for cocaine use will be randomized to: standard care (SC), SC + traditional reinforcement, or SC + progressive variable interval (VI) reinforcement. The two reinforcement interventions will provide the same overall average maximum magnitudes of expected earnings. Patients in the traditional reinforcement condition will earn reinforcers twice weekly for submitting stimulant negative samples. Patients in the progressive VI reinforcement condition will earn reinforcers for providing cocaine-negative urine samples according to an increasing VI schedule; monitoring and reinforcement will occur

relatively infrequently when abstinence is maintained but increase in frequency if drug use occurs. Cell phones will maintain contact with patients in all conditions to inform them of randomly selected urine testing days throughout a 24-week period to provide, for one of the first times, objective indicators of relapse following treatment cessation. All patients will complete cognitive assessments pre, mid and post-treatment.

Primary study aims are to:
1. Determine the efficacy of an adaptive progressive VI reinforcement intervention for reducing cocaine use in the short- and long-term.The hypothesis is that patients assigned to the adaptive progressive VI reinforcement intervention will achieve longer periods of abstinence than patients in standard care during the period reinforcement is in effect (24 weeks). We will also evaluate how well this reinforcement intervention maintains benefits throughout follow-up (18 months).

2. Compare the relative efficacy of adaptive progressive VI reinforcement to a traditional reinforcement intervention. Patients receiving adaptive progressive VI reinforcement are hypothesized to achieve greater during and post-treatment abstinence than those receiving traditional twice-weekly reinforcement.

Secondary and exploratory aims of the study are to:
a. Evaluate relations between behavioral and measures of cognitive control and response to monetary rewards and treatment outcomes. Patients with better cognitive control are expected to achieve longer durations of abstinence, regardless of treatment assignment. Patients who are more sensitive to monetary rewards are expected to achieve longer duration of abstinence, particularly when assigned to a reinforcement intervention. We also expect that sensitivity to monetary rewards and cognitive control may increase among those who are assigned to a reinforcement intervention, and that changes in these processes may mediate drug use outcomes.

b. Assess the impact of reinforcement interventions on HIV risk and other outcomes. Compared to SC, reinforcement interventions are expected to reduce high risk sexual behaviors that spread infectious diseases. Reinforcement interventions are also hypothesized to decrease psychiatric symptoms and improve quality of life. Both short-term and long-term effects will be examined. Gender effects will also be explored.

c. Estimate costs and cost-effectiveness. We will examine costs and cost-effectiveness of interventions and estimate conditions under which, and patients for whom, these interventions may be most cost-effective.

Results from this study will be highly relevant for policy decisions as reinforcement interventions move into practice settings. If adaptive progressive VI schedules are efficacious, this would be a major advance because this approach could be applied on a long-term basis to prevent relapse. This procedure minimizes patient and provider burden relative to traditional reinforcement interventions, and *even relative to typical aftercare interventions.* Moreover, as effective as reinforcement interventions may be, little is known regarding the types of individuals who do and do not respond to them. Inclusion of cognitive measures is likely to greatly enhance our understanding of predictors of patient response, which could lead to more efficient patient-treatment matching strategies. If this project yields evidence of pre- to post-treatment changes in cognition that mediate effects of reinforcement interventions, this information has the potential to revolutionize our understanding of how these very effective interventions exert their beneficial effects.

RESEARCH STRATEGY
Of all psychosocial treatments for drug use disorders, reinforcement interventions have the largest effect size (Dutra et al., 2008). Independent meta-analyses, spanning scores of studies, find reinforcement interventions consistently reduce drug use (Lussier et al, 2006; Prendergast et al, 2006). Given their strong evidence base, clinics across the US and internationally are beginning to implement these interventions. We have been at the forefront of addressing issues that impact dissemination of these interventions. Methods to reduce costs,

including the prize approach that we developed and assessed (Petry et al., 2000,2004,2005a) and tested in the NIDA Clinical Trials Network (CTN; Peirce et al., 2006; Petry et al., 2005b), have allowed integration in multitudes of settings. For example, Hospital and Health Corp. in NY successfully applied prize reinforcers in its clinics (Kellogg et al. 2005), RI, NY and SC have integrated reinforcers into drug abuse treatment (Henggler et al., 2008; McCorry et al., 2010; Squires et al., 2008), and England introduced reinforcers into its national health care system (Ballard & Radley, 2009; NICE, 2007; Pilling et al., 2007).

In support of these and other adoption efforts, we developed training materials, as well as adherence and competence indices, and demonstrated their relationships to patient outcomes (Petry et al., 2011a,2012bc). Clinicians readily can be taught to administer these interventions competently (Petry et al., 2010a, 2012bc; Squires et al., 2008), and prize reinforcement interventions are not only efficacious but also cost-effective when implemented clinically (Lott & Jencius, 2009; Olmstead et al, 2007abc, 2009; Sindelar et al, 2007ab).

A major development during our last period of support is that the Veteran's Administration (VA) called for use of reinforcement interventions nationwide (Schoenhard, 2011) and contracted with us to provide training and implementation support in >100 clinics. We trained clinicians (Rash et al., 2013), and >1000 veterans have received reinforcement, with clinician-- and patient-- response overwhelmingly positive (Petry et al., in press a).

Although highly efficacious while in effect, reinforcement typically ceases once patients discontinue care, when resumption of drug use is most likely. Methods to efficiently and effectively continue benefits after formal care ends are needed to prevent relapse and maintain effects. This is a critical scientific issue the present study is designed to address in that it will evaluate a novel reinforcement approach to extend long-term benefits.

Even though reinforcement interventions are notably efficacious, about 30%-50% of patients never achieve abstinence when exposed to them (Preston et al., 1998; Silverman et al., 1996; Weinstock et al., 2010). Little attention has been paid to evaluating variables related to response to these interventions. We will investigate predictors of response to these interventions, focusing on impulsivity and cognitive control.

Innovation

1. Extending benefits of reinforcement interventions. Reinforcement interventions are applied primarily during early stages of treatment. While clearly efficacious in this regard, a criticism has been that effects weaken once reinforcement stops. This is an issue with treatments in general, because most are provided on a brief and acute basis (McLellan et al., 2000). National guidelines recommend continuing care or aftercare after initial care (ASAM, 2001), but many patients do not present to aftercare or stop attending after few sessions and experience high rates of relapse (Dennis et al., 2003; Humphreys & Tucker, 2002; McKay, 2005; McKay et al., 2004; Simpson, 2004; SAMHSA, 2008). In community clinics, <15% of patients receiving standard aftercare complete 8 weeks, and over 75% relapse within 3 months of leaving care (Petry et al 2004,2005a,2006a).

Studies have investigated approaches to improve aftercare access and outcomes, including group sessions based on cognitive-behavioral (CB) principles and phone interventions (McKay, 2005). Although about half of aftercare studies found benefits relative to control or no interventions (McKay, 2009), more intensive and in-person interventions are not more effective than briefer or phone interventions (Coviello et al, 2001; McKay et al., 1997, 2005), and all suffer from poor adherence. McKay (2009, 2010) noted that key components of effective aftercare models are ones that: are low burden and convenient for patients; include aggressive attempts to stay in contact with patients; systematically monitor drug use; and use reinforcement.

Very few studies have evaluated reinforcement interventions as a means extending the benefits of care. Van Horn et al. (2011) used reinforcers to enhance participation in telephone care. They randomized 195 patients

who completed intensive outpatient care to telephone continuing care with or without reinforcers for participating in phone sessions. Patients receiving reinforcers completed 67% of calls versus only 39% for those without.

McKay et al. (2010) randomized 100 cocaine dependent patients who completed intensive care to 4 conditions using a 2 x 2 design: reinforcers for cocaine negative samples or not, and CB relapse prevention therapy or standard aftercare. Reinforcers significantly reduced positive samples and self reports of cocaine use, but no main or interactive effect of CB therapy was noted. Thus, reinforcement appears efficacious in preventing relapse during less structured phases of care. The addition of CB therapy failed to improve outcomes beyond reinforcers alone, suggesting that additional psychosocial interventions may not be necessary. However, access to reinforcers required frequent (3x/week) attendance, and patients find aftercare interventions that do not require frequent attendance to be more acceptable (McKay, 2009). Our progressive VI reinforcement intervention, outlined below, will allow for fairly infrequent attendance.

2. Adaptive progressive VI reinforcement should sustain effects. The progressive VI reinforcement intervention proposed here is novel because it adapts frequency of monitoring and reinforcing abstinence to the patient's progress as a means of sustaining benefits. Typically, monitoring and reinforcement schedules remain pre-set (e.g., twice weekly) and then are removed completely. However, basic behavioral research demonstrates that variable interval (VI) schedules of reinforcement are most likely to sustain change after reinforcers are removed (Ferster & Skinner, 1957; Nevin & Grace, 2000). In this study, patients initially will be reinforced for abstinence according to a usual twice-weekly monitoring system, validated in multiple trials (e.g., Petry et al., 2005b,2007a,2012bc). As long as patients maintain abstinence, the frequency of monitoring and reinforcing abstinence will decrease according to a VI schedule, gradually down to once every three weeks on average. If a patient submits a positive sample or fails to submit a sample, reinforcement will reset and frequency of monitoring increase until abstinence is re-instated.

This adaptive intervention is expected to increase the proportion of patients who receive large or full "doses" of reinforcement therapy. Less than half of patients in reinforcement interventions complete intended durations of care, even when they are only 12 weeks (Petry et al., 2004,2005ab,2006a,2011a,2012ab). In part, attrition from reinforcement interventions mimics discontinuation from standard care. Although reinforcement interventions enhance participation in clinical care relative to non-reinforcement treatments (Petry et al., 2005ab,2006,2011a,2012ab), patients stop providing samples and no longer receive reinforcers for abstinence once they cease attending groups. By encouraging patients who no longer attend group therapy to continue earning reinforcers for abstinence on their own self-selected and relatively minimal schedule, this progressive VI reinforcement intervention is likely to engage patients for longer durations. If efficacious, a VI schedule that adjusts to patient progress has the potential to change the course of how reinforcement interventions are implemented.

3. Cell phone technology will maintain contact with patients and inform them of testing schedules. Cell phones are increasingly applied in the context of health behaviors, and this study will use a novel approach to integrate cell phones into reinforcement interventions. Patients will receive unlimited cell service, highly desired because most patients with free plans use up allotted monthly minutes quickly. According to procedures worked out in prior trials (see prelim studies), patients will maintain use of study cell phones so long as they submit samples when contacted and asked to do so, regardless of results of the samples. This technology also provides a means by which staff can prompt sample submission and assess the natural course of relapse, and how it is impacted by reinforcement interventions, using objective indices even after patients cease attending treatment.

4. Neurocognitive assessment. This study is also novel in that it will evaluate neural processes underlying cognitive control and reward processing in the context of reinforcement interventions. Many neurobiological

models of addiction highlight the interaction between subcortical structures that mediate reward and cortical structures that support cognitive control (Everitt & Robbins, 2004; Everitt et al., 2008; Goldstein & Volkow, 2011; Koob & Le Moal, 2001; Volkow et al., 2003). We will investigate these processes and their relation to outcomes.

a.) Cognitive control. Deficits in cognitive control are a defining feature of addiction (Ersche et al., 2012; Goldstein & Volkow, 2011; Hyman, 2005), and the functions most commonly impaired (e.g., cognitive flexibility, inhibition, control, and attention) are the ones many treatments attempt to enhance (Sofuoglu et al., 2013). For example, learning new cognitive responses (e.g., to cravings) are critical aspects of cognitive-behavioral, motivational, and even 12-step approaches (Ersche & Sahakian, 2007; Garavan & Hester, 2007) (see Project #1). Reinforcement interventions, in contrast, rely on very basic learning principles. Such treatments have been applied for decades to individuals with severe cognitive dysfunction and mental retardation, for whom they are a standard of care (e.g., Bijou & Orlando, 1961). Because individuals with severely impaired cognitive functioning respond to reinforcement interventions, these treatments may be beneficial even among drug abusing patients with cognitive deficits, and data indicate that contingent rewards reliably and robustly sway decision making toward clinically desired behaviors (Dutra et al., 2008; Lussier et al., 2006). Nevertheless, drug using patients make choices between the alternate reinforcers provided by these interventions and the reinforcement provided by drug use. Such choices are made in patients' natural environments, where they experience cravings for drugs; when drugs become suddenly available, these choices rely on cognitive control, and the function of the prefrontal cortex (Kober et al., 2010; Volkow et al., 2010). Although cognitive control is not the primary tenet of reinforcement interventions, it may predict and contribute to treatment outcomes. Furthermore, patients practice acts of cognitive control by choosing to attend treatment and regulate craving, inhibit drug use, and maintain abstinence (DeVito et al., 2012; Muraven, 2010). Reinforcement interventions, especially if they result in continued use of these cognitive strategies while maintaining abstinence, may lead to greater cognitive control. Thus, cognitive control may be both a moderator and mediator of treatment outcomes (see prelim studies).

b.) Response to monetary rewards. Contemporary theories on addiction point to abnormalities in reward circuitry in regions such as the ventral striatum and ventromedial prefrontal cortex (e.g., Chau et al., 2004; Volkow et al., 2003). Volkow et al. (2003) have proposed that, in addiction, the reward value of drugs increases while the reward value of other reinforcers (such as money) decreases. Many studies have shown deficits in reward processing, reflected by reduced response to monetary rewards in the ventral striatum, in substance using patients relative to healthy controls (Balodis et al, 2012; Beck et al, 2009; Peters et al, 2011; Wrase et al, 2007). These findings appear especially relevant to reinforcement interventions, because they provide monetary rewards as alternatives to those derived from drugs. By their nature, these interventions may be particularly beneficial for those who are sensitive to monetary rewards. Therefore, we expect that individuals' neurocognitive responses to monetary rewards pre-treatment may predict treatment outcomes in reinforcement conditions, serving as a potential moderator of treatment effects. Further, because monetary rewards appear to serve as effective reinforcers at least as long as they are in effect, we expect that sensitivity to monetary rewards may increase during treatment, and that this increase may mediate outcomes.

5. Cost-effectiveness. We will not only evaluate the efficacy and moderators and mediators of these interventions, but also their cost-effectiveness, as we have done previously (Olmstead et al. 2007abc, 2009). These data will help inform decisions about for whom and under what circumstances funders or society may be willing to pay for their increased costs. As more private providers, state systems (NY, SC), and federal agencies (the VA) are integrating these interventions, this study will provide important and timely data regarding the conditions under which and patients for whom reinforcement interventions engender benefits.

Preliminary studies

We have conducted numerous studies showing benefits of reinforcement interventions, and data indicate--with great consistency-- that longer durations of abstinence are associated with long-term benefits. We completed a pilot study showing progressive VI schedules can maintain gains, and we have applied cell phones to prompt sample submission. Our pilot data also indicate that cognitive control and sensitivity to rewards relate to treatment outcomes during reinforcement interventions. Together, the data suggest that the proposed study is likely to yield hypothesized effects, and if so, an adaptive progressive VI schedule may have a

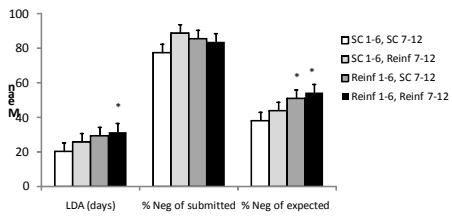
major impact on the future science and practice of reinforcement interventions.

A common criticism of reinforcement interventions is that effects wane once reinforcement ceases. These concerns, while valid, often do not acknowledge that some studies from our group (Alessi et al, 2007; Petry & Martin, 2002; Petry et al, 2005c; prelim studies) and others (Iguchi et al, 1997; Higgins et al, 2000a, 2003, 2007) **do** show benefits can persist after reinforcers are removed. Further, Higgins et al. (2000b,2007) and we (Petry et al, 2005a, 2006a,2007a,2010b,2011a,2012a) have consistently shown that a **robust predictor** of outcomes after reinforcers end is the longest duration of abstinence achieved.

An analysis of reinforcement studies from psychosocial/non-methadone clinics (Petry et al, 2004, 2005a, 2006a,2011a,2012a) suggests that longer durations of abstinence during treatment yield greater long-term benefits. Of 1074 patients randomized to a standard care or a standard care plus reinforcement intervention for 12 weeks, 1011 (94.1%) completed a 9-month follow-up and were coded as abstinent throughout 12 weeks of treatment and 9 months of follow-up (via urinalysis and self reports) or not (either index indicating use). Controlling for site, demographics (age, gender, education, race), and baseline drug use, longest duration of abstinence was significantly related to abstinence throughout the 9 month follow-up, Beta(*SE*)=.18(.02), Wald=91.61, *p*<.001, with each additional week of abstinence associated with a 19% increased chance of abstinence post-treatment (95%CI=1.15-1.24). Longer term exposure to reinforcement (24 in the proposed study vs 12 weeks in completed studies), in conjunction with the extended effects noted with VI schedules in general, should further increase durations of abstinence, arguably the best predictor of long-term outcomes.

We have pilot data suggesting that providing reinforcement for longer durations should increase abstinence. A total of 238 alcohol-dependent patients have been randomized to standard care (SC), SC+12 weeks of reinforcement for submitting negative breath samples, or SC+24 weeks of reinforcement for submitting negative breath samples. There is a strong linear association between time receiving reinforcement and longest duration of abstinence, whether abstinence is defined by negative samples alone, $F(2,235) = 6.75$, $p<.001$, or with self reports, $F(2,235)=6.75$, $p<.001$. On average, patients in SC achieved 7.8 $\pm$ 6.8 weeks of abstinence vs 10.5 $\pm$ 7.4 and 12.4 $\pm$ 8.5 weeks for those assigned to the 12 and 24 week reinforcement conditions, respectively.

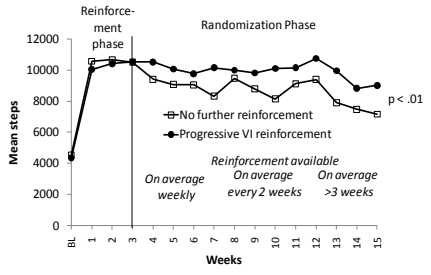
Our ongoing RCT was designed to isolate the best timing and duration of reinforcement. Preliminary analyses of 206 patients whose time in the study has elapsed reveal that longest duration of abstinence (LDA) is significantly greater in those receiving 12 weeks of reinforcement compared to those who were never reinforced ($p < .05$). Neither of the short-term (6 week) reinforcement interventions increased durations of abstinence compared to standard care. Results related to % negative samples submitted vary depending on how missing data are included. When number of submitted samples is the denominator, no differences exist between groups with >80% testing negative. When expected samples are included in the denominator, % negative samples is higher in patients receiving reinforcement throughout 12 weeks, or just for the first 6 weeks (ps < .05) relative to those in SC. These between-group differences depending on how missing samples are considered likely relate to differential sample submission rates across groups. Patients in all conditions receive $2/sample submitted, and mean samples obtained is 10.5, 11.5, 13.7 and 14.8 in the SC 1-6/SC 7-12, SC 1-6/Reinf 7-12, Reinf 1-6/SC 7-12, and Reinf 1-6/Reinf 7-12 conditions, respectively. The latter two conditions differ from patients receiving SC for the entire 12 weeks in sample submission rates ($p < .05$). To more fully identify potential benefits, it is critical to obtain higher and equal rates of sample submission across groups, which provision of cell phones should do.



Thus, reinforcement interventions—when applied during early stages of care—are efficacious, with the most consistent and long-term benefits in those exposed to reinforcers for longer durations.

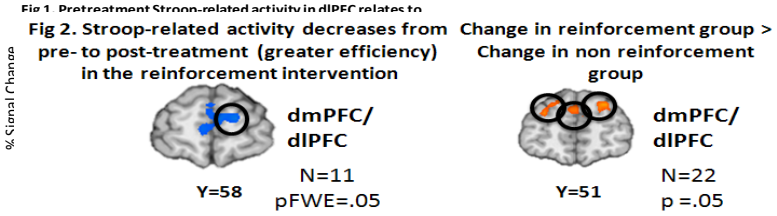
Although reinforcement is beneficial, only 33% of patients assigned to the longest duration reinforcement condition completed a full course of 12 weeks of treatment, with median time in treatment being 5 weeks. Nevertheless, 82.1% of patients continued submitting samples beyond their time in treatment when a modest $2 per sample was provided. These results suggest that the proposed study, which will arrange greater overall compensation for sample submission via cell phone service, will be able to obtain even higher rates of sample submission and more accurately gauge drug use. Further, willingness to submit samples after discontinuing formal treatment bodes well for an adaptive reinforcement intervention that maintains contingent reinforcement even after patients cease attending group therapy sessions. By requiring less frequent attendance with a progressive VI schedule, we expect to increase the proportion of patients who remain involved in the reinforcement intervention.

We have data showing that a **progressive VI schedule can maintain behavioral gains when delivered relatively infrequently**. Exercise, similarly to drug abstinence, is a behavior that is difficult to initiate and sustain. We provided pedometers to sedentary adults (mean steps/day at baseline was 4,400) and encouraged them to walk ≥10,000 steps/day. For 3 weeks, participants attended the clinic 2-3 times/week according to a set schedule, similar to those used in drug abuse treatment studies that reinforce abstinence. As in our drug abuse treatment trials, these participants earned draws with chances of winning prizes each day they walked ≥10,000 steps. At week 4, participants (N=61) were randomized to no further reinforcers or progressive VI reinforcers, in which frequency of monitoring and reinforcing walking decreased down to once every three weeks on average. In weeks 4-15, each participant selected two potential monitoring days (M-Th, M-F, or T-F) and they were phoned each of those mornings and informed whether or not they needed to attend the clinic that day for pedometer uploads (identical to procedures planned herein). Participants attended 88.6%±18.7% of requested sessions, with no differences in attendance or days of pedometer data available between groups, p = .58. At sessions, participants randomized to the progressive VI condition earned prize draws if the past 4 days of pedometer data indicated walking ≥10,000 steps per day. A missed session or a day in the past 4 days with <10,000 steps resulted in no draws, and a reset in draws the next time they were randomly selected to attend. As shown, participants randomized to VI reinforcement maintained gains more than participants who ceased earning reinforcers after the initial reinforcement phase, p<.01. Thus, this progressive VI reinforcement procedure was efficacious in maintaining high rates of behavior even when infrequent (and low magnitude) reinforcers were arranged. Over the 12-week randomized phase, a mean of $77±$68 in prizes ($6/week) was sufficient to sustain high rates of walking. Given promising results in altering physical activity and its strong basis in basic behavioral research generally, a similar progressive VI schedule is likely to be efficacious in maintaining abstinence in cocaine dependent patients, a hypothesis this study will test directly.

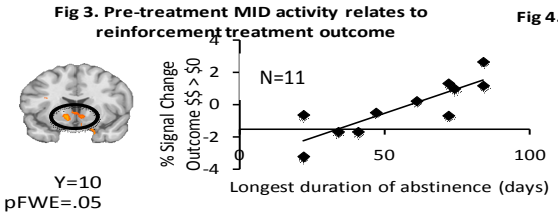


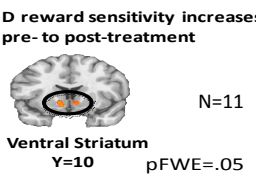
We have fMRI pilot data from Carroll et al.'s (under review) trial relevant to reinforcement interventions. Pre- and post- treatment imaging data from the Stroop task (described in DeVito et al., 2012) were obtained from 22 cocaine dependent patients. Eleven were randomized to a reinforcement intervention, and 11 to a non-reinforcement intervention; all 22 received placebo medication. Two main findings emerged: 1) Greater pre-treatment Stroop activity in the dorsolateral prefrontal cortex (dlPFC) was positively correlated with reinforcers earned in those receiving the reinforcement intervention, suggesting that better cognitive-control pre-treatment may be related to better response to treatment (Fig 1). 2) Stroop activity decreased in dmPFC and dlPFC from pre- to post-treatment in those receiving the reinforcement intervention, and these effects were greater among those in the reinforcement than the non-reinforcement condition (Fig 2). We reported similar decreases in these regions in concert with improvements in Stroop performance, suggesting greater efficiency in these PFC circuits (DeVito et al., 2012) and consistent with findings noted with working memory training (Klingberg, 2010). Together, these data suggest that Stroop-related activation in the PFC may relate to outcomes, and that reinforcement interventions may be associated with changes in brain functioning in these

regions.



The Monetary Incentive Delay (MID) task is commonly used to assess neural activity during anticipation and receipt of monetary rewards (Balodis et al., 2012). Neural activity is compared between no reward ($0) and reward conditions ($5) during a period of anticipation, and once the outcome is revealed (winning $5 or $0). Compared to controls, those with drug use disorders have reduced neural response to monetary rewards in regions including the ventral striatum (VS; Andrews et al., 2011; Balodis et al., 2012; Goldstein et al., 2007). MID data are available from the 11 cocaine-dependent participants above who received a reinforcement intervention. As expected, greater pre-treatment activity in the VS during receipt of monetary rewards (outcome phase) was associated with longer abstinence during treatment (Fig 3). We also observed increases in activity in the VS pre- to post-treatment in patients receiving the reinforcement intervention (Fig 4).





These data suggest that reward-related activation in the ventral striatum, which has been implicated in drug effects and reward processing more generally, may predict treatment outcomes in reinforcement interventions, and these interventions may be associated with increased sensitivity to monetary rewards over time. These data, however, are from a small sample, and MID data were only available from participants randomized to the reinforcement intervention (Unfortunately, multiple subjects assigned to the non-reinforcement intervention experienced technical difficulties or excessive movement during participation in the MID task, problems we have since corrected). The proposed study will examine these associations with an adequately powered sample, comparing patients receiving reinforcement and standard care interventions.

Methods

Design: This 3-group randomized design will address two primary scientific questions: (1) will adaptive progressive VI reinforcement improve short- and long-term abstinence outcomes compared to standard care, and (2) will adaptive progressive VI reinforcement yield benefits beyond that of traditional reinforcement?

Subjects and setting: Patients will be recruited from admissions to intensive outpatient care at Alcohol & Drug Recovery Centers (Hartford, CT), Hospital of Central CT and Farrell Center (both New Britain, CT), Carlson Recovery Centers (Springfield, MA), Regional Network of Programs (Bridgeport, CT), and The Village (Hartford, CT). Use of multiple clinics enhances generalization of findings and has worked well (Petry et al., 2011a,2012ab). Clinics provide comprehensive services, including intensive day programs and long-term aftercare. They were selected because they have similar treatment approaches and intensities of care, and treat analogous populations.

A subset of patients assigned to SC and SC+adaptive VI reinforcement groups (n=30 per group) who do not meet exclusion criteria for imaging will be offered participation in an fMRI sub-study. Pre- and post-treatment scans will be conducted at Hartford Hospital Institute of Living's Olin Neuropsychiatry Research Center.

Inclusion criteria: Each subject must: (1) be age ≥ 18 years, (2) have a current DSM-5 cocaine use disorder diagnosis, and (3) be willing to sign informed consent and able to pass an informed consent quiz.

Exclusion criteria: are (1) serious, uncontrolled psychiatric illness (e.g., schizophrenia, bipolar disorder, or suicide risk), (2) in recovery from pathological gambling, or (3) do not speak English.

Exclusion criteria for the fMRI sub-study are: (1) current use of any medication that affects blood flow (e.g., for hypertension) and (2) any conditions that are contra-indicated for fMRI scanning: claustrophobia, presence of ferromagnetic metallic implants, prior severe head trauma, color blindness, left handedness and pregnancy (assessed via urinalysis on day of scanning). See Human Subjects.

Informed Consent: Patients who meet inclusion, but not exclusion, criteria will be offered the chance to participate in the study within 7 business days of clinic admission. Research assistants (RA), under PI supervision, will obtain consent, prior to collection of any study data. Anyone who does not participate in the study will receive standard care (Human Subjects). A separate consent will be used for the fMRI sub-study and the decision to participate in the sub-study will have no bearing on participation in the main study.

Assessments. After informed consent, subjects will undergo a 2-3 hr evaluation (that may be split over 2 days) to evaluate inclusion and exclusion criteria, primary and secondary outcomes, and possible moderators and mediators of effects. Assessments were selected based on their psychometric properties and theoretical and/or empirical association with reinforcement interventions and drug use treatment outcomes. Measures will be collected at BL, and those that change over time throughout months 1,3,6,9,12,15, and 18 as shown. Patients receive $35 in gift cards for the BL assessment, and $50 for all others, plus $25 in gift cards for computer/impulsivity assessments (as well as the chance to win an additional $5 based on task responses). Those eligible for fMRI will receive $100 for the pre- and post-treatment scan.

- DSM-5 criteria Checklist (DSM) (APA, 2013) assesses alcohol, cocaine, methamphetamine, opiate, benzodiazepine and marijuana use disorder.
- The NODS assesses DSM-IV pathological gambling with good reliability and validity (Gerstein et al, 1999).
- Shipley Institute of Living Scale (Zachary, 1991) is included as a measure of general intelligence.
- The Addiction Severity Index (ASI; McLellan et al., 1988) provides ratings on alcohol, drug, medical, legal, psychiatric, employment, and social functioning. Psychometric properties are well established (Cacciola et al., 1997; McLellan et al., 1985; Zanis et al., 1994). Brief sections on cigarette smoking and demographics are also included. An abbreviated version will be administered at follow-up.
- The Brief Symptom Index (BSI: Derogatis, 1992) is a widely used 53-item inventory of psychiatric symptoms that asks participants to rate items on a 5-point scale of distress and is used across protocols to monitor psychiatric symptoms.
- State-Trait Anxiety Inventory (STAI) is a widely used measure of both consistent and transient stress and anxiety (Kendell et al., 1976) and is included as a potential moderator of treatment effects.
- Quality of Life Inventory (QOL; Frisch et al., 1992) assesses satisfaction with and importance of life areas (work, health, recreation, etc) and is positively impacted by reinforcement interventions (Petry et al., 2007b).
- HIV Risk Behavior Scale (HRBS;Darke et al., 1991) measures injection and sexual risk behaviors reliably and validly (Petry, 2001b), which decrease in reinforcement interventions (Hanson et al, 2008; Petry,et al., 2010a,2011a). Non-overlapping items on the Risk Assessment Battery (Navaline et al., 1994) will be included. The HRBS will assess lifetime at baseline, past month at the Month 1 interview and the past 3 months at all other timepoints, including baseline.
- The Risk Assessment Battery (RAB; Navaline et al., 1994) is a comprehensive assessment of risk behaviors (e.g., Chaudhury et al., 2010; Disney et al., 2006; Takizawa et al., 2007; Tourian et al., 1997). Questions from the RAB (that do not overlap with the HRBS) will assess lifetime and past 3 months at baseline, the past month at the Month 1 interview and the past 3 months at all other timepoints.

- The Service Utilization Form (SU; Olmstead et al., 2007) will be used to evaluate services received and costs. An abbreviated version will be administered at follow-up.
- The Timeline Follow-back (TLFB; Sobell et al., 1980) uses calendar prompts to elicit specific information about the frequency and intensity of substance use over time intervals with good test-retest reliability and validity (Sobell & Sobell, 1992). It will assess days and quantity of alcohol use and days of cocaine, amphetamine, methamphetamine, opioid, benzodiazepine, marijuana or other drug use 3 months before treatment, throughout treatment, and since the last interview at follow-up.
- CANTAB: Our principal set of cognitive tasks is drawn primarily from the Cambridge Automated Neuropsychological Test Battery (CANTAB) (www.cambridgecognition.com). CANTAB is a well-validated computerized battery designed to be sensitive to a broad range of cognitive abilities, ages, education levels and cultures (e.g., primarily language-independent; Robbins et al., 1998). The software allows for accurate timing, secure data storage, quick data access and processing. For many tasks, age-, gender-, and IQ-adjusted normative databases are available, and reports as to a subject's performance relative to such norms can be immediately generated at the end of testing.
- Balloon Analog Risk Task (BART) is a computerized measure of risk-taking (Lejuez et al., 2003). We have found it to be predictive of response to specific treatments in several projects (Carroll et al., 2011).
- Personality inventories include Barratt Impulsiveness Scale (BIS;Patton et al., 1995), which contains three subscales (cognitive, non-planning and motor impulsivity), and
- Eysenck Personality Inventory (EPI;Eysenck et al., 1985).
- Delay discounting (DD) is assessed by choices between immediate and delayed money (Bickel et al.,1999;Petry, 2001ac).
- Probability discounting (PD) evaluates preferences for certain vs probabilistic money (Andrade & Petry, 2011; Kirby & Marakovic, 1996; Madden et al., 2009). (One of six possible versions of the PD (versions A-F) will be randomly selected by the roll of a die for each participant at baseline and post-treatment evaluation.)
- For Iowa Gambling Task (IGT;Bechara et al., 1994), in a computer-administered format, subjects select from card decks that vary in probabilities and magnitudes of gains and losses, and main outcome is choices from gain decks with smaller short-term rewards.
- Urine and breath samples will be tested for alcohol, cocaine, amphetamine, methamphetamine, marijuana, benzodiazepine and opioids via standardized procedures, and clinic records will be accessed to validate days attended treatment.
- fMRI tasks will include the Stroop Color-Word Interference Task to assess cognitive control as well as neural activity (Egner & Hirsch, 2005; MacLeod, 1991; Streeter et al., 2008) and
- the Monetary Incentive Delay Task (MIDT) to assess responsivity to monetary rewards (Andrews et al., 2011; Balodis et al., 2012; Jia et al,, 2011).

fMRI Task	Primary Domain	Description	Relevance	Neural Correlates	Hypothesized Pharmacological Moderators
Monetary Incentive Delay Task (MIDT)	Reward Processing	Respond with button press to target on screen in order to win or avoid losing money	Individuals with addictions (cocaine, tobacco, alcohol, gambling) show differences from those without in brain function during MIDT with links to treatment outcome	Ventral striatum, vmPFC, insula, amygdala and others	DA, NE, ACh, GABA, Glu, 5-HT
Stroop Color-Word Interference Task	Cognitive Control	Appropriately name color of ink when it is matched ("blue" in blue ink) or mismatched ("blue" in red ink) to spelled work.	Individuals with cocaine dependence show differences in performance and brain activations linked to treatment outcomes	ACC, dlPFC, insula, thalamus, striatum, midbrain and other regions	DA, NE, ACh, GABA, Glu, 5-HT

Assessment	BL	During Tx (wk 1-24)	M1	M3	M6	M9	M12	M15	M18
DSM,NODS,Shipley	X								
ASI,BSI,STAI,QOL,HRBS, RAB, SU	X		X	X	X	X	X	X	X
BART, BIS, EPI,DD, PD, IGT	X			X	X				X
CANTAB	X			X	X				
TLFB	X	X	X	X	X	X	X	X	X
Urine and breath samples	X	Up to 2x wkly	X	X	X	X	X	X	X
Clinic attendance	X	Up to daily	X	X	X	X	X	X	X
fMRI (subset; n=60)	X				X				

Follow-up assessments will be *scheduled* to take place about 1, 3, 6, 9, 12, 15 or 18 months from study intake and other study visits will be *scheduled* as described below. However, in this study population, patients are often difficult to contact (e.g., homelessness, unstable housing) or become unavailable to meet (e.g., in controlled environment). We have many procedures in place to address these issues (e.g., collection of contact information, reminder calls and cards, etc.). Given these difficulties, some flexibility in scheduling is required to protect participants from unnecessarily limiting study procedures to a specific calendar day. If a participant misses a study visit or follow-up evaluation, research staff will attempt to contact and reschedule, but, we anticipate late and missed appointments. Study visits may be conducted over the phone or by mail if needed.

During the COVID-19 outbreak and until exposure risks to participants and research assistants are reduced, study visits will be completed over the phone. Participants who complete follow-up visits over the phone will miss some components (i.e. sample submission) but will receive the full $50 follow-up payment. If the interval between the remote follow-up and opportunity to collect samples/measures is minimal, participants may be able to submit these missed components after risk decreases. Payments for completed mailed packets will remain $30.

Incarceration: This is a minimal risk study that recruits non-prisoner patients from substance abuse treatment programs. However, a portion of the study patients are likely to be incarcerated during the study period due to illegal activities that are common in this population. If a patient is incarcerated during study participation, all study procedures are suspended except the evaluations. In the ICF, patients indicate whether or not they would like the evaluation questionnaires sent to them in prison. The mailing delivered to the incarcerated patient only contains the evaluation questionnaires and a cover letter indicating the questionnaires are follow-up to a study the patient participated in at the University of Connecticut Health Center. A stamped and addressed return envelope is also provided with the questionnaires. If the patient completes and returns the questionnaires for Month 1, 3, 6, 9, 12, 15 or 18, they will receive $30 in the form of a check. The patient will receive the check after their release from incarceration or they may designate a person to whom the check should be sent during their incarceration. The patient is notified in the ICF that their participation in this study while incarcerated will have no effect on their eligibility for parole.

Randomization: Patients will be randomly assigned to one of the three conditions. An urn randomization program (Stout et al., 1994), will balance patients based upon baseline sample results (cocaine positive or negative) and whether or not they were in a controlled environment in the past month (e.g. jail, inpatient detoxification). These variables are used because initial toxicology results are a strong predictor of outcomes (Petry et al., 2004; Preston et al., 1998; Stitzer et al., 2007), and controlled environments impact drug use. A separate 'urn' will be employed in each clinic, thereby stratifying on clinic as well.

A. Standard treatment (weeks 1-24): Patients assigned to this condition will receive standard care, consisting of group therapy, including daily planning, 12-Step therapy, relapse prevention, coping and life skills training, recreation training, focus groups for depression and anxiety, and AIDS education. Intensity starts at 3-4 groups

per day 3-5 days per week and is gradually reduced to 1 aftercare group per week. Individual and family counseling is provided on an as-needed basis, usually only for crises. Groups are led by recovering individuals, nurses, and MA level counselors. Format and intensity of care is similar across clinics.

Study patients will undergo regular urine and breath sample monitoring for 24 weeks. In the first three weeks, twice weekly testing will be arranged, coinciding with early and late weekdays of clinic attendance (M-Th, M-F, Tu-Fri). Thereafter, days selected for sample collection will be randomly selected from patients' twice weekly preferred schedule (M-Th, M-F, or T-F), which may or may not coincide with group therapy, as some patients will have ceased attending groups. RAs will phone or text (patient's preference) on the morning of each testing day to inform them whether or not to leave a sample that day. For example, in weeks 4-9, a patient with a M-F schedule may be asked to come in on Mon, Mon, Fri, Mon, Fri, Mon in the respective weeks. Patients will be told to plan to leave a sample on each of their test days, and will be phoned or texted on average every other possible test day in weeks 4-9 and told they need not leave a sample that day. In weeks 10-24, days for sample collection will reduce to once every 2-3 weeks on average. Patients need only avail themselves for sample collection on two days per week (beginning and end of each week), and the schedule of availability can change over the 24-week period (e.g., from M-Th to T-F) so long as patients give at least one week notice. Patients will receive $2 per requested sample submitted, plus a $20 bonus if they submit all requested samples in a four week period (regardless of results). In the case of an excused absence, patients can come in the next day to submit a sample and still be eligible for the $20 bonus.

To ensure contact and submission of samples on requested days, patients will receive a study cell phone (allowing unlimited calls and texting) as long as they do not miss more than one requested sample in a row. If a patient fails to submit a sample on a testing day, the RA will phone the patient that afternoon/evening and remind him/her that if s/he fails to provide a sample the *next* selected testing day, the phone will be turned off. After a missed sample, the next two test days will be prompted for sample submission. For example, if a patient failed to submit a sample when requested on a Mon, that patient would be prompted for another sample that Thur, and the following Mon. If the patient missed the Thur sample (or any two prompted samples in a row), cell service would be discontinued. The goal is to obtain on average $\geq$18 samples from patients across 24 weeks and equivalent samples relative to Group C, so that objective indices of drug use will be available similarly across conditions. (To accommodate for the potential of higher test days that may occur in Group C patients who relapse, additional test days will be randomly selected based on running averages of samples obtained from patients in the adaptive condition; Dr. Andrade has developed and maintained programs to automate sample selection days in ongoing and pilot trials). This system encourages submission of samples to accurately and consistently gauge drug use, without being unduly burdensome.

Although some patients have their own cell phones, >90% of those with phones have pre-paid or government-limited plans, resulting in highly unreliable service (most quickly use up all their minutes). In an informal survey, 93% stated that patients would submit samples up to twice weekly for 6 months in exchange for unlimited cell service. Patients who prefer to use their own cell may elect to receive a $25 gift card for each month during which they do not miss more than one randomly selected test day in a row. (Patients with their own phones may switch to study phones at any time to ensure contact). If a study phone is turned off, it will be reinstated as soon as the patient submits a sample (i.e., the patient comes to the clinic or UCHC to submit a sample on their own, without being prompted to do so). After discontinuation of cell service, patients will be informed in writing about how to reinstate it. Once cell service is reinstated, similar rules related to continued use will be applied (and service discontinued if they miss >1 prompted test day in a row).

As in all our studies, research will be separate from clinical care. The clinics rarely test for drug use, and only upon suspicion. Clinic-requested samples will occur separately from research samples, and results not shared, as arranged previously (Petry et al., 2011a,2012a). RAs will congratulate patients for each drug for which they test negative, and if positive, encourage them to discuss any use in group (Human Subjects).

We expect that most patients will not continue in treatment at the clinics for 24 weeks, and median length of stay is <5 weeks. Although prompting sample submission via cell phones will increase sample submission, we expect any effect related to enhancing clinic group attendance will be modest. For >15 years, patients in our studies have been returning to clinics for study procedures (sample submission, follow-ups),

which are clearly differentiated from treatment procedures. Even if these procedures do enhance clinical services received, the effects will be similar across groups as all receive the same incentives for sample submission (i.e., cell service).

B. Standard care + twice weekly reinforcement for abstinence: Patients assigned to this condition will receive standard care and urine sample monitoring as above. As in Group A, patients will receive $2 per requested sample submitted, plus a $20 bonus if they submit all requested samples in a four week period (regardless of results). In the case of an excused absence, patients can come in the next day to submit a sample and still be eligible for the $20 bonus. These patients will also draw from an urn and have a chance to win prizes each day they provide a stimulant negative urine sample according to their twice-weekly testing schedule. For the first stimulant negative sample provided, they will earn one draw from a prize bowl, and the number of draws earned will increase by one for each consecutive negative sample submitted up to a maximum of 5 draws per negative sample (after 3 weeks of abstinence). If ever a patient fails to leave any of their twice weekly samples or submits a positive sample, draws earned the next time they leave a negative sample will reset to 1, and then escalate as before. Excused absences (medical or court appointment arranged in advance with therapist, and verified emergencies, e.g., car broke down with tow receipt) will not reset draws.

The urn will contain 500 cards, and 50% of them will be winning cards. Of these, 204 will be small prizes (patient's choice of $1 coupons, toiletries, food items, or bus tokens); 45 will be large prizes, worth up to $20 in value (choice of CDs, gift cards, watches), and one will be a jumbo prize up to $100 (choice of stereo, TV, or five larges). Cards are replaced after each draw, so that chances of winning remain constant. A variety of prizes will be kept in a locked cabinet, and when patients win they chose a prize from that category. This schedule provides similar probabilities and magnitudes of prizes as our prior studies (Petry et al., 2004,2005abc,2006a, 2007a,2011a,2012abc). Patients have an expected maximum average earning of 229 draws (mean expected earnings of $460 in prizes) if they submit all 48 negative urine samples over 24 weeks.

Patients in this condition, as in Group A, will receive a study cell phone (or $25/month toward their own cell phone service) if they maintain contact with research staff and submit samples when requested to do so. Because the reinforcement schedule for abstinence is set at twice weekly for 24 weeks, there is little reason to inform patients of reinforcement days throughout the study period. However, RAs will phone or text patients at the same frequency in this condition as in Groups A and C to inform them when "a sample is due to maintain cell phone service." If they fail to submit a sample when prompted, additional samples will be requested within the next week, as described in Group A. If two requested samples in a row are missed, then cell service will be discontinued. Reinstatement of cell service will be as described above.

In this manner, reinforcement for submission of negative samples is similar to that provided in traditional reinforcement interventions (pre-determined frequent urine testing). At the same time, prompting of urine sample submission (along with cell phone service for complying with submission) will be similar to other groups so that overall the same minimum number of samples should be obtained across conditions. In this manner, objective indicators of relapse to drug use will be obtained similarly across groups (see also Analyses).

Patients in this group can earn draws for providing negative samples in response to a cell phone prompt, and they may not have submitted these samples had they discontinued care in a traditional reinforcement intervention. In this sense, Group B is somewhat enhanced relative to traditional reinforcer interventions, and allows for a conservative test of Aim 2. Nevertheless, maximum draws per sample is only 1 when patients fail to submit negative samples twice weekly in this condition. Thus, the additional reinforcement for submission of samples by integrating cell phone prompted samples appears modest and unlikely to impact outcomes.

C. Standard care + progressive VI reinforcement. These patients receive standard care and earn draws with chances of winning prizes for submitting negative urine samples. However, relative to Group B, the frequency with which they are expected to submit samples to earn abstinence reinforcement decreases over time so long as they maintain abstinence. In the first phase, twice weekly samples are expected just like the other groups,

with sample collection days occurring at the beginning and end of the week and coinciding with regular clinic attendance (when applicable) and patient preference for days (M-Th, M-F, or T-F). Once patients in this group achieve ~3 weeks of continuous abstinence, they will be expected to submit samples on average once a week for the next 6 weeks (phase 2). After 9 full weeks of abstinence, sample collection will decrease to every other week on average for the next six weeks (phase 3), and finally patients who maintain abstinence will be transitioned to a testing and reinforcement schedule of every three weeks on average for the final 9 weeks of the 24-week treatment period (phase 4). In total, an average of ≥18 samples will be scheduled over 24 weeks in patients maintaining abstinence. As in Groups A and B, patients will receive $2 per requested sample submitted, plus a $20 bonus if they submit all requested samples in a four week period (regardless of results). In the case of an excused absence, patients can come in the next day to submit a sample and still be eligible for the $20 bonus.

As in Group B, patients earn 1 draw per negative sample, and draws earned increase by one draw for consecutive negative samples during the twice-weekly testing phase (phase 1). To accommodate for the reduced overall number of samples submitted relative to Group B and to maintain overall equal maximum reinforcement between conditions, once a patient moves to the phase 2 sample schedule (once a week) draws per negative sample increase by 2 draws for each consecutive negative sample provided. Draws continue to increase by 2 up to a cap of 25 draws per negative sample, which would be achieved after about 15 weeks of abstinence.

If a patient fails to provide a sample or submits a positive sample, draws earned for the next negative sample reset to one, and then increase by one per consecutive negative sample. The frequency of testing and reinforcement also increases after a reset to rapidly reinstate abstinence. After a missed or positive sample, the patient will be asked to submit samples on all scheduled testing days for 2 consecutive testing days, earning 1 and then 2 draws if negative. Then, sample collection will resume to weekly on average for about another 2-3 weeks (earning 3, 4 and 5 draws if negative). Upon achieving 5 draws (~4 weeks of abstinence), number of draws earned will reinstate back to the highest level previously attained for the next negative sample, and sample collection frequency will coincide with whatever level the patient was previously at. In other words, a patient who had previously achieved 13 weeks of abstinence and was at every other week random testing would resume 21 draws per negative sample and every other week random testing once he has attained a month of abstinence following a lapse or missed sample. Using this schedule, patients who test negative on all test days will earn about 231 draws over the 24-week period, similar to Group B. As in other conditions, RAs will congratulate patients for each substance for which they test negative, and encourage them to discuss any use in group.

Design considerations:

Why these reinforcement parameters? The parameters were chosen to be consistent with reinforcement schedules found previously efficacious and to equally reinforce abstinence in the two reinforcement conditions. The total number of draws possible is nearly identical (±2 draw) across conditions, and within each phase of reduced monitoring and reinforcement in Group C, overall possible reinforcement is similar to that in Group B. The continued escalating feature of reinforcement in Group C accommodates for the reduced frequency of testing and reinforcement, such that instead of earning 5 draws per negative sample twice a week, patients earn about 10 draws once per week. When further tapered to less than weekly testing, draws possible remain at about 20-25 draws every 2-3 weeks. Although this number of draws may appear to be a lot, it takes only about 2 min to select and open 25 slips, which translates to an expected average earning of about $40 in prizes.

Why this testing frequency? A gradually decreasing frequency was selected to balance clinical, practical, and scientific considerations. In the first few weeks, some patients will not yet have achieved abstinence, and twice-weekly testing will detect all (or most all) drug use. Once abstinence is achieved, it does not appear necessary to monitor drug use as frequently, and random tests will ensure that use does not occur around known testing times. The schedule outlined should detect relapse as mean frequency of cocaine use is 10

days/month (Petry et al., 2012a), i.e., 2.5 days/week, which is likely to be detected at the next randomly selected testing day even during infrequent testing phases. Importantly, informing about testing and reinforcement days could be automated (computerized phone systems prompting samples) and continue long term (e.g., for ≥1 year) as a cost effective method to maintain abstinence if this study finds this intervention effective while it is in place. In contrast, requiring patients to come to a clinic twice weekly for 24 weeks (or longer), while also potentially efficacious, adds substantially to staffing and testing costs, as well as reinforcement costs.

Will patients submit samples after leaving treatment, and will compensating sample submission confound results? We have conducted studies in which patients were compensated for providing samples after leaving formal care (Petry et al., 2011a; prelim studies), and patients continued providing samples even when no longer engaged in clinical care. In an informal survey, 93% stated that patients would submit samples up to twice weekly for 6 months in exchange for unlimited cell service. Strict separation of treatment and research is maintained, with clinic staff encouraging engagement in research activities after treatment ends. If a patient were uncomfortable returning to the clinic after ending care, alternate locations for sample collection or evaluations can be arranged (see Human Subjects). Compensating patients for leaving samples or attending follow-ups increases those specific behaviors, but it has not impacted clinic attendance when research and clinical aspects are kept distinct; further, compensation for study procedures will be identical across groups.

What if reinforcement is effective in the short- but not long-term? We anticipate adaptive progressive VI reinforcement will be more likely than standard care (and even typical reinforcement procedures) to yield post-treatment benefits because it is likely to engage more patients in the reinforcement intervention longer and engender longer periods of abstinence, which is consistently linked with post-treatment outcomes (Higgins et al., 2000b; Petry et al., 2005a,2007a,2010b,2011a,2012ab). However, if long-term benefits do not occur, the adaptive reinforcement intervention could be maintained (even indefinitely in high-risk populations) to sustain benefits. Reinforcement once every 3 weeks on average is a low intensity intervention that may ultimately be a highly effective, relatively low cost maintenance approach applicable to a wide range of behaviors, including weight loss, medication adherence, exercise, and diabetes management (Petry et al,2011b,2012d, in press de). It is also less intensive than other forms of aftercare (1 hour weekly groups), requiring only 10 min of staff time.

Are interventions generalizable? Twice-weekly reinforcement interventions are already being implemented in clinics, as noted earlier. Although this adaptive progressive VI schedule is more complex, schedules of testing and reinforcing can be computerized and reminders set via cell phones, as we are doing (R21-DA029215, R01-HD075630). This system reduces frequency of monitoring as patients achieve more sustained periods of abstinence, similarly to methods of monitoring patient outcomes in other chronic diseases. For example, when blood pressure or A1cs remain in clinically accepted ranges, medical appointments are minimized, but when objective indices indicate difficulties in maintaining goals, intensities and frequencies of treatment increase. The National Business Group on Health (2013) reported that 85% of employers are now using reinforcers to promote health behaviors, and section 2705 of the Affordable Care Act allows employers to use up to 50% of total premiums for outcome-based incentives. Thus, insurers and society are recognizing the potential of reinforcement interventions to positively impact outcomes of diseases with behavioral components. Clinics, if appropriately reimbursed, could prompt, collect, test, and reinforce samples every 3 weeks from patients, even after they discontinue participation in traditional group therapy. This VI reinforcement intervention minimizes patients' and providers' time, thereby ultimately increasing potential for generalization.

Data Quality Control: Separation of clinical (treatment) and research components (structured evaluations) is critical. One RA will manage the reinforcement system, and another, blind to treatment conditions when possible, will conduct structured evaluations when possible. The project director will supervise implementation of treatments, assessing adherence and competence, and ensure equal and appropriate sample prompts

across conditions. Checksheets will be kept, listing data collected, draws earned and prizes won; sessions are audiotaped and reviewed for competence (Petry et al,2010a,2012bc).

Data Analysis. An important issue preceding analyses is to identify baseline differences between groups despite random assignment. Differences between groups that may be related to outcome (e.g., psychiatric diagnoses, dependence severity, clinic services received) will be used as covariates or fixed factors, as appropriate. Analysis will be conducted on an intent-to-treat basis, using all randomized patients, and both short-term (changes from baseline to month 6) and longer-term (throughout the 18-month follow-up) efficacy will be evaluated. The primary outcome is longest duration of cocaine abstinence, a continuous variable that can be transformed if needed. Groups will be compared using t-tests for normally distributed data, or ANCOVA if covariates are included. The design includes 3 treatment groups, allowing for analyses of two main effects.

Primary aim # 1 is to examine the efficacy of adaptive progressive VI reinforcement. We will compare those randomized to Group C vs Group A with respect to longest duration of abstinence during the 24-week intervention period and throughout the 18-month follow-up period.

Primary aim #2 is to assess if adaptive reinforcement improves duration of abstinence achieved relative to traditional reinforcement. We will compare those randomized to the two reinforcement conditions with respect to during treatment and long-term abstinence outcomes.

Secondary aims are to evaluate the impact of the interventions on other indices of stimulant and secondary drug use outcomes. Using the same contrasts above, we will compare groups with respect to: proportions of submitted and expected samples that test negative for stimulants and other drugs (alcohol, opioids, THC), and subjective reports of use (SUC % abstinent days). The first rely on objective indicators and such data will be available from all randomized patients. Subjective reports will supplement objective indices, and patients can be considered using if either index is positive. In terms of proportional data, missing samples will be considered missing (not impacting the denominator) in one analysis, and positive in another to consider the range of possibilities with respect to drug use outcomes. Because Group B has more expected samples (48) than the other groups ($\geq$18), proportional data for expected samples will rely upon the cell phone prompted samples ($\geq$18), designed to be similar across conditions, to conservatively test group differences.

Power analyses for primary aims. Our studies reinforcing abstinence generally find Cohen's *d* effect sizes of 0.6 to > 1.0 for during treatment drug use outcomes (Petry et al, 2000, 2002,2004,2005abc,2006a, 2007a,2010b,2011a,2012abc). In terms of post-treatment effects, our ongoing study is finding an effect size of 0.46 for a 12-week reinforcement intervention in enhancing post-treatment abstinence relative to standard care. Although we expect a larger effect size when 24 weeks of reinforcement is provided, and especially if more patients engage in the adaptive progressive VI reinforcement intervention for greater durations, we will conservatively power this study to detect a similar effect size of 0.46 between the VI reinforcement intervention and standard care for long-term outcomes. Using a Type I error rate of α=.05, a Type II error rate of β=.20, and power=0.80 (Cohen, 1988), 60 patients/ group are needed to detect *d*=0.46 between the standard care and reinforcement interventions (Aim 1). For Aim 2, the study is powered to detect a lower, but still clinically meaningful, effect size of 0.35 between the two active reinforcement conditions, similar to effect sizes found between reinforcement conditions in other studies (Petry et al., 2004, 2006a). Using the same power analyses outlined above, 110 patients/group are needed to detect $d \geq .35$ between the traditional and adaptive reinforcement conditions with respect to during treatment and long-term outcomes. Thus, we will recruit 280 patients (60 in standard care and 110 each for the reinforcement interventions).

Secondary aims are to evaluate if reinforcement improves other indices of drug use, psychosocial functioning (ASI, BSI scores), quality of life, and HIV risk behaviors, as found in other studies (Ghitza et al., 2008; Hanson et al, 2008; Petry et al., 2007b,in press b). These are continuous measures, with missing data likely. If no systematic differences in missing data are noted (the case in our prior studies), hierarchial linear models (HLM; Gibbons et al., 1993) using MIXREG (Hedeker, 1993) will analyze differences between groups over time. These analyses have advantages over repeated measures ANOVA as they estimate missing data via model parameter

estimates and use real time, rather than scheduled time, of assessments. Two contrasts will be explored. One will evaluate Aim 1, assigning a contrast weight of +1 to patients in VI reinforcement and –1 to standard care. For aim 2, we will assign contrast weights of +1 to those receiving adaptive reinforcement and –1 to traditional reinforcement. Analyses will be conducted for both short- (BL to M6, with up to 4 data points/ patient: BL,M1,M3,M6) and long-term effects (BL through M18, with up to 8 data points/patient: BL,M1,3,6,9,12, 15,18). The model will include factors for group (using contrasts above), time, and the interaction of group by time. These analyses will ascertain whether the interventions impact areas of functioning beyond drug use.

Changes in other drug use over time can also be examined using urinalysis data. Means of $\geq$18 samples will be scheduled for collection over 24 weeks, and $\geq$22 samples through the M18 follow-up. Samples will be coded as positive for any illicit drug or negative for all substances. HLM using MIXOR (Hedeker, 1996), an HLM program for dichotomous measures, will examine group changes over time, using contrasts above.

Moderators of effects will be explored. To date, we have investigated gender as a moderator of effects but never observed gender effects on drug use outcomes in reinforcement studies (e.g., Petry et al., 2005ac, 2006a,2010b,2011a,2012a), perhaps in part because we provide highly desired prizes for both men and women (Petry, 2012). Nonetheless, effects of gender will be explored, as will interactions between gender, treatment condition, and other characteristics that may impact outcomes. Although we do not anticipate gender differences in main outcomes, we expect to find gender-specific HIV risk behaviors (Barry et al., 2008; Rash & Petry, 2009). We have also found that women show greater heritability of impulsive responding on cognitive tasks than men (Petry et al., 2002) and women with addictive disorders and ASPD are particularly impulsive (Andrade et al., under review).

To determine if patient factors predict outcome, multiple regression analyses will be used to find predictors of continuous measures (e.g., longest duration of abstinence, percent negative samples), and logistic regressions for dichotomous dependent variables (e.g., presence or absence of stimulant use at follow-up). Cox regression analyses may also be used to determine what factors predict time to event outcomes, such as time to first positive sample after study initiation. Independent variables will include treatment condition, site, days attended groups at the clinic, drug use severity (ASI-drug scores, baseline positive samples), scores on cognitive control tasks at baseline (computer task or impulsivity scores), and demographics, including gender and race. Analyses will be conducted for the entire sample and with interactions of predictors with condition to assess if certain characteristics are more predictive of outcomes in the different treatment conditions.

Behavioral changes that result from treatment may also be a function of improving cognitive control, and reinforcement interventions may lead to reductions in drug use by enhancing cognitive functioning. If effects of reinforcement on drug use outcomes are significant, cognitive control as assessed via computer and impulsivity tasks will be evaluated as a potential mediator of effects. A latent growth model using structural equation modeling can be built. Models will be built sequentially, starting with a basic latent growth model comprising drug use days over time, modeled as slope and intercept. Important cognitive performance indices can be tested as mediators in turn. A bootstrapping resampling procedure will estimate model test statistic *p* values and parameter standard errors (Arbuckle, 2006). Models will be considered to fit the data if the chi-square is not significant, Comparative Fit Index (CFI) is >.97, and root mean square error of approximation (RMSEA) is <.10 (Bollen & Long, 1993) using an iterative basis, with individual paths added or deleted on the basis of modification indices (Jöreskog & Sörbom, 1984). Once a basic latent growth model is determined, treatment group will be added as a predictor of slope and intercept. Then, cognitive variables (pre to post change scores) included in the model. Beta weights of the full model can be tested using a product of coefficients test to determine if mediation is significant (MacKinnon 2007a,b).

The fMRI sub-study will provide refined tests of hypotheses related to cognitive control in a subsample. The Stroop effect is calculated as the difference in reaction time between incongruent and congruent trials. In fMRI data, it is defined as difference in neural activity between incongruent and congruent trials.

1. To evaluate relationships between pre-treatment behavioral and neural measures of cognitive control during the Stroop task and treatment outcome, we will assess the Stroop effect and related neural activity and correlate these indices with treatment outcomes (e.g., longest duration of abstinence, % negative urines).

2. To assess changes in behavioral and neural measures of cognitive control, we will compare indices pre- to post-treatment (e.g., (Incongruent(pre) > congruent (pre)) > (Incongruent(post) > congruent (post)). We will also compare these indices between groups to identify treatment-specific changes.

The MID task allows examination of neural activity during anticipation and receipt of monetary rewards. Anticipation of reward is assessed by comparing neural activity during the reward anticipation phase, and contrasting conditions of $0 and $5 (Anticipation of $5>$0). Responses to receipt of monetary rewards are assessed by comparing neural activity during the outcome phase (Receipt of $5>$0).

1. To examine relationships between pre-treatment behavioral and neural measures of reward processing and treatment outcome, we will assess neural responses during anticipation and receipt of reward ($5>$0) and correlate these indices with treatment outcomes (longest duration of abstinence, % negative urines).

2. To evaluate the change in response to monetary rewards from pre- to post- treatment, we will compare indices from this task from pre- to post-treatment (e.g., anticipation of $5 pre>post, and receipt of $5 pre>post). We will also compare differences in these indices between groups to identify treatment-specific changes.

For cost and feasibility issues, the fMRI study is limited to patients in groups most likely to show treatment differences, Groups A and C. This design most cost-effectively addresses the issue of if, and how, the availability of monetary based reinforcers alter brain functioning. Based on our earlier work (Devito et al., 2012; Kober et al., 2010) and pilot data, we estimate a medium effect size for changes in regions such as VS and PFC regions. Thirty participants per group is sufficient to determine correlations of $r \geq .30$ between neural activity in Stroop and MID task and outcome variables. We estimate 25 participants post treatment will be sufficient to assess treatment-related changes in neural activity over time (see Devito et al., 2012).

If effects of reinforcement interventions are moderated by cognitive control, future studies may target these interventions toward patients based on cognitive functioning. As reinforcers add known costs, being able to determine those who will be most positively affected will help direct scarce resources toward patients most likely to benefit. If cognitive function mediates outcomes, future research may refine and test therapies that reduce impulsive choices, and improve cognitive flexibility, inhibition and/or control (Bickel et al., 2011). Combining reinforcement with an intervention that improves cognitive control may result in even more durable effects, which may reduce personal-- and societal—harms related to drug abuse.

Economic Evaluation. If primary hypotheses are supported, we will conduct cost-benefit analyses. These interventions can be costly, even when reinforcers are relatively modest. Not only must costs of reinforcers be included, but so must administration costs, which include staff time for managing and delivering reinforcers. Despite costs, these interventions may provide benefits to (1) clinics in terms of enhanced reimbursements (Lott & Jencius, 2009), and (2) society in terms of reductions in healthcare services (hospitalizations, ER visits) and criminal justice system costs, and improvements in workplace productivity (Petry et al., in press c). Using data from the PAC-SAT, this study will determine the net benefit of adding reinforcers, from both clinic and societal perspectives. It will also estimate costs of each week of abstinence attributable to the reinforcement conditions.

a. Comprehensive administrative costs of interventions will be quantified (Olmstead et al., 2007abc;

Rosenheck et al, 1995; Sindelar et al. 2007ab), including costs of prizes, mileage for purchasing them, and toxicology tests and management (personnel time to arrange testing and reinforcers in both reinforcement conditions, along with costs of cell phone service in the adaptive reinforcement condition only). Costs related exclusively to data collection (arranging for collection and testing of urine samples when it is not reinforced, RA salaries for data collection) will not be included, as they would not be relevant if interventions were applied clinically. Costs for usual clinical services and clinic reimbursement for same will be ascertained.

b. General healthcare costs will be estimated by multiplying service units used per patient by average unit costs. In- and out-patient, day hospital, aftercare and emergency room services will be estimated from CT claims data, and nationally from the Market Scan database, which estimates service costs.

c. Criminal justice (CJ) system costs. Patients receiving reinforcement interventions may have reduced involvement with the CJ system. The PAC-SAT assesses services provided as well as police contacts, court hearings, and incarceration, along with timing of events that resulted in service use so acts occurring before study participation can be separated from those occurring during it in terms of resource utilization. Unit costs of services will be estimated from national reports (Pastore & Maguire, 2003; US Dept. of Justice 2006).

Other societal costs will be obtained on productivity (earnings and workdays affected by drug use) and automobile crashes (including property damage, injuries, and fatalities).

Calculation of net benefits. First, resource utilization and cost data will be used to estimate the average net benefit (i.e., benefits – costs) per patient in each intervention from clinic and societal perspectives (Drummond et al., 2005; Zarkin et al., 2008). Second, average net benefits, and confidence intervals around estimates, will be calculated by subtracting average net benefit of adaptive reinforcement from standard care, or adaptive from traditional reinforcement. Finally, sensitivity analyses (Olmstead et al., 2007a; Drummond et al., 2005) will determine the robustness of the net benefit to alternative assumptions about a variety of cost parameters (e.g., unit costs of services, reimbursements received). If reimbursements rise by maximizing the number of patients attending groups via reinforcement treatment, net benefits are higher as shown by Lott and Jencius (2009).

Cost-effectiveness ratios. If reinforcement engenders net benefits, then it ought to be adopted. However, even in the absence of a net benefit, the incremental cost-effectiveness ratio (ICER) is critical to eventual policy decisions. The ICER is calculated as: (i) incremental costs to (ii) incremental effectiveness (difference between average effectiveness of treatments in terms of weeks of abstinence). Using expert panel recommendations (Gold, 1996; Johanneson, 1996; Weinstein, 1996), we will present traditional ICERs and uncertainty of the ratios (Gold, 1996; O'Brien et al., 1994) and derive a single synthetic measure of multiple indicators of effectiveness, including quality of life (Hargreaves et al., 1997; Rosenheck et al., 1998). We will also conduct acceptability curve analysis to provide policy relevant interpretations (Fenwick et al, 2001,2004; Lothgren & Zethraeus, 2000; Polsky et al., 1997; vanHout et al., 1994). Multiple samples are selected randomly (bootstrapped), with replacement, from the original sample to approximate the larger population. These analyses can also be performed with important subsamples, such as patients with greater sensitivity to rewards if this is determined to be an important predictor of response to reinforcement interventions. Incremental cost and effectiveness values and ICERs can be calculated for each new sample and compared with theoretical "willingness to pay" values for an outcome, such as days abstinent. Such analyses inform policy makers in decision-making (Olmstead et al, 2007ab; Sindelar et al, 2007b) and can be conducted with samples even smaller than those herein (Olmstead et al., 2007c,2009; Sindelar et al., 2007a).

In sum, this study allows for rigorous determination of costs and benefits of interventions that accrue to clinics and society. A clinic perspective is crucial because, at least in the immediate future, agencies are unlikely to fund expanded services unless they are cost beneficial. Societal perspectives (ICER analyses) are critical for future policy that might allocate state and federal funding to further support reinforcement interventions, as is now being done on a limited basis for substance abuse care as well as in some other health care arenas. Only a comprehensive study such as this can address multiple perspectives, ranging from individual differences in cognitive response to treatments, to clinical and societal effects. The ultimate goal of this proposal, which integrates these perspectives, is to optimize benefits of reinforcement interventions and extend them to the patients most likely to derive clinically significant, and durable, reductions in drug use.

Human Subjects

1. RISKS TO THE SUBJECTS

a. Human Subjects Involvement and Characteristics.

i. Inclusion Criteria.

Subjects will be 280 men and women, age 18 and older, who meet DSM-5 criteria for cocaine use disorder and who are beginning intensive outpatient treatment at a community-based substance abuse treatment clinic. All subjects must be willing to sign informed consent and must be able to pass (6 or more correct responses) a brief, 8-item quiz inquiring about study procedures, such as "Do you get to choose which treatment group you go into?" and "Can you drop out of the study at any time and still come to regular treatment at this clinic?" In our past studies, only rarely have potential subjects failed to pass this quiz, which ensures understanding of study procedures.

Participants with substance use disorders in addition to cocaine may participate in this trial to enhance generalization of findings; the vast majority of patients with cocaine use disorders have more than one substance use diagnosis. These clinics do not offer outpatient treatment services to patients experiencing physiological withdrawal symptoms, and such patients will have been referred to, and completed, an alcohol detoxification prior to initiating the intensive outpatient treatment program from which this study will recruit.

ii. Exclusion Criteria.

Exclusion criteria are serious uncontrolled psychiatric illness (acute bipolar disorder, schizophrenia, or suicidal behavior); in recovery from pathological gambling or current pathological gambling diagnosis and desiring to stop or reduce gambling (because of potential concerns of similarity of prize reinforcers and gambling even though no increases in gambling have been reported; Petry & Alessi, 2010; Petry, Kolander et al., 2006); and do not speak English (all treatment is provided in English at these clinics so we expect no patients who present to these clinics to be disqualified based on the language criteria; local clinics provide substance abuse treatment services in other languages).

Participants in the main trial will be invited to participate in the fMRI sub-study associated with this project following randomization to Groups A or C. Only patients assigned to these two groups will be offered participation in the fMRI sub-study to conserve costs associated with fMRI; these two groups are expected to show the greatest differences with respect to treatment outcomes and hence are also expected to show the greatest pre to post differences with respect to neural changes during treatment. Participants interested in the fMRI sub-study will be screened and excluded from the fMRI sub-study for current use of any medication that affects blood flow (e.g., for hypertension) and for any conditions that are contra-indicated for fMRI scanning: claustrophobia, presence of ferromagnetic metallic implants, prior severe head trauma, color blindness, left handedness, and pregnancy (assessed via urinalysis on day of scanning).

iii. Ineligible Patients.

Some patients will choose not to enroll or will not qualify for the main study. These patients may continue receiving standard services at the clinic in which they are enrolled, and they may also be referred to their treatment provider or other facilities (e.g., other substance abuse treatment clinics, mental health treatment facilities, or to a gambling treatment clinic such as Problem Gambling Services in CT) as appropriate.

Similarly, some participants in the main trial will be ineligible for or not want to participate in the fMRI sub-study. Prospective participants will be informed that declining the invitation to participate in the neuroimaging component will not affect their ability to participate in the main trial or their ability to receive treatment at the clinic or elsewhere.

iv. Treatment Clinics, Services, and Patient Population.

Patients will be recruited from Alcohol & Drug Recovery Centers (Hartford, CT), Hospital of Central CT and Farrell Center (both New Britain, CT), Carlson Recovery Centers (Springfield, MA), Regional Network of Programs (Bridgeport, CT), and The Village (Hartford, CT). These centers all provide comprehensive substance abuse treatment services, including an intensive day program and long-term aftercare. The clinics were selected because they have similar treatment approaches, provide equal intensities of care, and treat analogous patient populations.

At each clinic, about 8-12 patients enter the intensive day program each month from which subjects for this study will be recruited. Intensive outpatient care (up to about 6 hours/day, 3-5 days/week) is provided for 3-4 weeks (depending on need), and then partial care (2-6 hours/day, 2-3 days/week) for another 2-4 weeks. Level of care is gradually reduced to 1-2 group/week during aftercare. Aftercare is recommended for 12 months, although very few patients continue attending treatment for this duration of time. About 40-60% of patients entering each clinic have a cocaine use disorder; the remainder have primarily an alcohol or marijuana use disorder. For over 15 years, we have been conducting similar studies at these and other community based clinics and the clinics have never encountered a problem meeting recruitment goals or integrating studies in the context of standard care; non-study patients are intermixed with study patients within the same group sessions without problems because the reinforcement intervention and study procedures are implemented on an individual basis, and at least half the patients in treatment at the clinics are not involved with the study.

b. Sources of Materials. Research material includes interviews, questionnaires, audiorecordings of interviews and sessions, abstraction of attendance data from clinical charts, and observation of patients by study staff. Breath samples and urine samples will be tested for evidence of alcohol and illicit drugs, e.g., stimulants (cocaine, amphetamine and methamphetamine), opioids, benzodiazepine and THC. None of these materials will be available to legal, educational, or employer representatives. Data obtained for research purposes will be at no cost to patients. Urine and breath samples obtained for study purposes will not be shared with clinical staff except in the case of an emergency (patient deemed a threat to himself or others). Electronic data are stored on password-protected secured computers in locked facilities.

   Sources of material for the fMRI portion (for those eligible) will include performance measures on the tasks (e.g., Stroop, MID), and the MRI data collected. The performance measures will be collected via computer as will the MRI data during scanning on a 3T magnet. Electronic data are stored on password-protected secured computers in locked facilities.

c. Potential Risks. Risks associated with participation in this research study include the following:
   i. Disappointment if participants are not assigned to their preferred treatment group;
   ii. Discomfort from being asked questions about alcohol and drug use, medical problems and histories, HIV risk behaviors, psychosocial problems, and submitting breath and urine samples;
   iii. Difficulties that may arise from discontinuation of study cellular phone service if patients fail to submit requested urine samples.
   iv. Potential breach of confidentiality.
   v. Risks associated with participating in the fMRI sub-study are considered minor as it is a non-invasive procedure and does not involve any radiation, but include the hazard from loose metal objects and feelings of claustrophobia associated with all MR imaging of the head.

2. ADEQUACY OF PROTECTION AGAINST RISKS

a. Recruitment and Informed Consent.

Study patients will be recruited from individuals initiating treatment at one of the participating centers. All potential clients will receive an explanation of the study protocol, its potential risks and benefits, and alternative treatment available. Following resolution of any questions, patients who pass a brief quiz regarding the nature of the study and consent to participate will be asked to sign the study consent form and HIPAA document. A signed copy of the consent and HIPAA forms will be given to each patient. As noted above, patients who choose not to participate in the study or who are deemed ineligible for it will receive standard services at the center and may also be referred elsewhere for services if indicated.

An opt-in statement regarding audiorecording in the consent form will be utilized for recording of the interactions between research assistants and study participants, including baseline and follow-up interviews. These audiorecordings are utilized only for quality insurance procedures, to rate research assistants according to set standards in interview and treatment administration. Patients may participate in the study even if they do not choose to allow audiorecording of the interviews (in our prior studies, less than 10% of patients refuse audiorecording). The audiorecording consent form will explain that the purpose is to rate the research assistants' interviewing skills.

Recruitment for the fMRI sub-study will be separate from the main study, utilizing a unique informed consent form as relates to this sub-study. After completing the baseline assessment and being randomized as part of the main study, those who are assigned to Groups A and C, and who appear to possibly be eligible for fMRI will be screened for the fMRI sub-study, and additional fMRI exclusionary criteria assessed. Those who do not meet fMRI exclusionary criteria, and who choose to participate in the fMRI sub-study after receiving full informed consent for the fMRI study, will then be scheduled for fMRI. Patients may choose not to participate in the fMRI sub-study and still continue in the main study, as well as receive standard care at the clinic. Decisions whether or not to do the fMRI study will have no bearing on the primary study, or non-study, procedures.

b. Protection Against Risks. The following will protect against potential risks:

i. Random group assignment is used so that patients have about a 78% chance (220 of 280) of being assigned to a reinforcement group (60 of 280 are in the standard care condition; see power analyses), and patients may voluntarily end study participation if they are dissatisfied with their assignment.

ii. The interviews and sample collections are brief, patients may skip questions or take a break if uncomfortable, and the particular sample assays chosen are intended to minimize discomfort. All participants will be informed (in the informed consent form and at each visit) that in weeks 1-3, they will be expected to submit urine samples twice weekly, according to their own pre-set schedule at the beginning and end of each week (M-Th, M-F, or T-Th). To maintain cellular phone service, they cannot miss more than one requested sample in a 7-day period. Participants will be informed that in weeks 4-24, they will be phoned or texted (their preference) each morning of their twice weekly possible testing days and told whether they need to submit a sample that day. If they fail to submit a requested sample, they will be phoned and/or texted later that same afternoon and told that they MUST submit a sample when requested at the next testing day to maintain cellular service. The consent form will state explicitly that all study participants will be asked to submit between 15 and 35 samples in weeks 4-24 to maintain cellular service, that failing to provide a sample when requested will result in the need to provide samples

on the next two consecutive testing days, and that missing two requested samples in a row will result in a discontinuation of cellular service.

iii. Participants will be informed of how to reinstate cellular service in the consent form and after any missed sample (i.e., if they submit a sample, discontinued service will be reinstated within about 24 hours). Additionally, if cellular service is discontinued, they will be contacted, informing them of the process about how to restore cellular phone service (i.e., submit a sample). If patients are uncomfortable returning to the treatment clinics to submit samples, they can also submit samples at UCHC, which is on the bus lines from Hartford and New Britain. Patients will be also informed in the consent form that if they wish to alter testing days they can do so at any time with one week's notice.

iv. All data will be coded by number, not name, and a "key" form will be kept in a separate locked file cabinet. No information will be provided about the patients enrolled in this study to anyone outside of the clinical and research teams, except in emergency situations (e.g., severe intoxication, participant deemed a threat to him/herself or others) or as required by law. Locators (identified by patients to assist in finding them if needed for follow-ups) will not be given <u>any</u> information regarding the participant's treatment status, only that we are trying to reach them regarding their participation in a health study.

Digital audio recordings of interviews and sessions will be stored as .wma files. All recordings will be labeled by number, not name, and the "key" form will be kept separate in a locked file cabinet. These files will be transferred from the digital recorder to a secured folder on the UCHC network drive after the recording is completed. This folder will only be accessible to research staff. Once files are transferred to the secure folder, they will be deleted from the recorder itself. When not in use, recorders will be stored in locked cabinets with data. Subjects will not be identified by name on recordings. Only study personnel will review the recordings for training, supervision, and adherence monitoring purposes. We will obtain consent to audiorecord, and patients may participate in the study without allowing audiorecording. The .wma files will be permanently deleted at the end of the study.

Any study participant who arrives at the clinics grossly intoxicated is not provided any clinic services that day. This project will strictly adhere to these clinic rules, and patients who appear to be intoxicated or smell strongly of alcohol will not be allowed to participate in group or individual therapy, or complete follow-up evaluations. Such patients will be immediately referred to clinic staff (e.g., clinic director) and/or asked to leave the center. If the patient is deemed a threat to him/herself or others, police or emergency personnel will be contact to assist in the situation as required by law. Almost none of the patients who attend these centers have automobiles, but any patient who may have driven to the center will be requested to provide their keys to clinic personnel. If they refuse, police or emergency services may be contacted, as required by law.

v. To protect participants who are eligible and agree to participate in the fMRI portion of the trial, all participants will be screened for appropriateness for fMRI using a screening form. All participants will be screened using a screening form for any metallic objects that they may be holding or have implanted in their bodies and all potential participants with metallic implants will be excluded. Individuals with occupational histories that might pose problems for MRI will be required to undergo additional safety procedures (e.g., individuals who have performed welding without eye protection will be required to obtain orbital x-rays prior to scanning). Similarly, other potential sources of metal (e.g., tattoos that contain magnetically sensitive metals), along with pregnancy will be investigated for compatibility with MRI. The Screener will be repeated prior to imaging to ensure that

participants are not bringing any metallic materials into close proximity of the magnet, where they might be pulled toward the magnet or heated by the magnet. As a routine part of neuroimaging, individuals are also required to walk through a metal detector prior to entering the room with the scanner.

Further, on the day of scanning, information about menstrual cycle (for women), tobacco use (for smokers, including pre- and post-scan carbon monoxide (CO) assessments), alcohol use (pre- and post-scan breathalyzer measures) and substance use (urine toxicology and self-report) will be obtained. Participants who are smokers will be given the opportunity to smoke about one hour prior to scanning in order to avoid acute intoxication or withdrawal effects from tobacco. Consistent with our prior fMRI studies, participants who are experiencing acute drug intoxication or withdrawal will not be scanned. Similarly to data from the main trial, all fMRI data will be coded by a unique code, and not names. Electronic data are stored on password-protected secured computers and paper information with PHI linked to the computerized data is kept secured in locked file cabinets in locked facilities

c. Potential Benefits of the Proposed Research to the Subjects and Others. The anticipated benefits to patients in the study include careful evaluation of their medical and psychiatric status, drug and alcohol use, and a potential for reducing their cocaine use. Patients in all groups will receive $35 in gift cards for the baseline assessment, and $50 for all others, plus $25 in gift cards for computer/impulsivity assessments (as well as the chance to win an additional $5 based on task responses). Patients will receive $25 for returning the cell phone in working condition. They will receive a study-paid cell phone (or $25 per month in the form of gift cards to be given at the 3 and 6 month assessments, if they choose to use their own phone, for a total of $150) so long as they provide study-requested samples, estimated average of 18-23 per patient. Depending on group assignment, patients may also receive prizes for submitting stimulant negative samples.
Payment for participation in the fMRI sub-study is $100 per completed session, pro-rated to $20 per hour for incompleted sessions, to a maximum of $200 in total for two completed sessions.

Benefits to society include a potential improvement in the effectiveness of treatment for patients with substance use disorders.

d. Importance of the Knowledge to be Gained. The potential risks of these treatments are minor compared to the risk incurred by patients with cocaine use disorder. The risk/benefit ratio appears favorable.

e. Women/Minorities/Children. We expect the gender and racial composition to reflect the demographics of the clinic members. About 50% of patients at each clinic are female, and >45% are members of ethnic minorities (30% African American and 15% Hispanic, all of whom are fluent in English as treatment is only provided in English at these clinics, and 2% Native American, Asian American, or other). These proportions allow for exploratory analyses of gender and racial/ethnicity effects, as we have done previously (e.g., Montgomery et al., 2012).

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