Cover Page

Official Title: The Long-Term Treatment of Drug Addiction and Unemployment

NCT Number: NCT02487745

Document Date: 3/06/2022

1. Abstract

Drug addiction is as a chronic relapsing disorder. High magnitude and long-duration voucher-based abstinence reinforcement is one of the most effective treatments for drug addiction and can maintain cocaine abstinence over extended periods of time, but practical methods of implementing these interventions are needed. Workplaces could be ideal and practical vehicles for arranging and maintaining abstinence reinforcement over long time periods. Our research on a model Therapeutic Workplace has shown that employment-based abstinence reinforcement, in which participants must provide drug-free urine samples to maintain maximum pay, can maintain cocaine abstinence. Now we need to develop effective and economically sound methods to arrange long-term exposure to employment-based abstinence reinforcement. We are proposing evaluate the effectiveness and economic benefits of a Wage Supplement Model of arranging long-term exposure to employment-based abstinence reinforcement. Under this model, successful Therapeutic Workplace participants are offered abstinence-contingent wage supplements if they obtain and maintain competitive employment. Governments have used wage supplements effectively to increase employment in welfare recipients. The Wage Supplement Model harnesses the power of wage supplements to promote employment, while simultaneously using the wage supplements to reinforce drug abstinence. The intervention will combine the Therapeutic Workplace, Individual Placement and Support (IPS) supported employment, and abstinence-contingent wage supplements. IPS is a supported employment intervention that has been proven effective in promoting employment in adults with severe mental illness. Under this model, participants will be exposed to the Therapeutic Workplace to initiate drug abstinence and establish job skills. To promote employment and prevent relapse to drug use, participants will receive IPS Plus Abstinence-Contingent Wage Supplements. A randomized trial will evaluate the effectiveness and economic benefits of the Abstinence-Contingent Wage Supplement Model in promoting employment and sustaining cocaine abstinence in low-income unemployed injection drug users who continue to use cocaine during opioid agonist treatment (N=120). Participants will be enrolled in the Therapeutic Workplace for up to 3 months and then randomly assigned to an IPS Only group or an IPS Plus Abstinence-Contingent Wage Supplement group for one year. IPS Only participants will receive the IPS intervention. IPS Plus Abstinence-Contingent Wage Supplement participants will receive the IPS intervention and abstinence-contingent wage supplements. Drug use while participants are employed in community jobs may be monitored by American Substance Abuse Professionals, Inc. (ASAP®), a leading provider of workplace substance abuse services in the U.S. This novel intervention could be an effective and economically sound way to promote long-term cocaine abstinence and employment in injection drug users, a population at risk for many adverse outcomes because of their poverty, unemployment and injection drug use.

In a secondary study to be done in collaboration with the NIDA IRP, participants will also undergo ambulatory monitoring of mood, behavior, and geolocation. The aim is to follow up on prior findings from the IRP that, unlike the general population, people in addiction recovery may experience work as a respite from stress.

2. Objectives

The project will have the following primary and secondary objectives:

Primary Objectives. Assess the effectiveness of the IPS Plus Abstinence-Contingent Wage Supplements in increasing competitive employment and preventing relapse to heroin and cocaine use.

Secondary Objective: Proximal and Distal Risk Factors. Assess the effectiveness of the IPS Plus Abstinence-Contingent Wage Supplements in reducing drug-related risk behaviors (proximal) and reducing family poverty (distal).

Secondary Objective: Post-Intervention Effects. Assess the effectiveness of the IPS Plus Abstinence-Contingent Wage Supplements in promoting long-term drug abstinence and employment and in reducing HIV risk.

Secondary Objective: Economic Analyses. Assess the costs, cost-effectiveness and cost-benefit of IPS Plus Abstinence-Contingent Wage Supplements relative to IPS Only.

Secondary Objective: Ambulatory Monitoring through Geographical Momentary Assessment (GMA). Replicate and extend prior findings that people in addiction recovery may experience work as a respite from stress rather than a stressor. Assess relationships among mood, drug craving, behavior, and activity space in Therapeutic Workplace participants compared to delayed work group, and across time in all participants.

3. Background

Drug addiction can be a chronic problem that can persist for many years and sometimes throughout a person's lifetime (Dennis et al., 2007; McLellan et al., 2000). Treatments can promote drug abstinence in some patients, but relapse is common after treatment (Knapp et al., 2007; Lancaster et al., 2006; Sees et al., 2000; Veilleux et al., 2010). Many individuals achieve periods of drug abstinence that last a year or more, but still relapse (Galai et al., 2003; Shah et al., 2006). The development of enduring solutions to sustain abstinence over many years is perhaps the greatest challenge facing the substance abuse treatment research community. This project seeks to develop a long-term treatment to address the chronic relapsing nature of drug addiction.

Treating Injection Heroin and Cocaine Use in Low-Income, Unemployed Adults

This project will focus on low-income, unemployed injection drug users who use heroin and cocaine. Injection drug users are targeted because they are at elevated risk for HIV (CDC, 2012), hepatitis (Daniels et al., 2009), criminal activity (Hakansson et al., 2012; Novak et al., 2011), and overdose (Marshall et al., 2011). We will focus on low-income, unemployed individuals because they are at increased risk for injection drug use (Armstrong, 2007; Novak et al., 2011; Roberts et al., 2010) and for adverse consequences of injection drug use, including HIV (CDC, 2012). We are focusing on heroin and cocaine use because they are injected and because they are primary drugs that are injected in Baltimore (Novak et al., 2011; Shah et al., 2006).

Treating heroin and cocaine addiction in injection drug users. Many injection drug users use both heroin and cocaine (Leri et al., 2003). Methadone and buprenorphine can reduce heroin use (Shah et al., 2006; Veilleux et al., 2010), but many methadone and buprenorphine patients use cocaine (Castells et al., 2009) and no pharmacotherapy effectively treats cocaine addiction (Karila et al., 2011). Cocaine use in injection drug users is associated with HIV (CDC, 2012) and persistent injection drug use (Shah et al., 2006).

Addressing the chronic nature of injection heroin and cocaine use. Injection drug use tends to persist, and recurs even after long periods of abstinence (Shah et al., 2006). Opioid agonists can promote heroin abstinence, but they must be maintained to maintain effects (Sees et al., 2000). A reviewer of cocaine addiction treatments concluded no treatment resolves "the chronic, relapsing nature of addiction (Knapp et al., 2007)."

Contingency Management Interventions for Persistent Cocaine Users

Contingency management interventions, in which patients receive desirable consequences contingent on providing objective evidence of drug abstinence, may be the most effective psychosocial treatments for drug addiction (Castells et al., 2009; Dutra et al., 2008; Knapp et al., 2007; Pilling et al., 2007). These interventions are rooted in research that suggests drug addiction is operant behavior that is maintained and modifiable by its consequences and should be modifiable through the strategic use of reinforcement (Bigelow et al., 1999).

Voucher-based abstinence reinforcement. One of the most effective contingency management interventions is voucher-based reinforcement in which patients receive monetary vouchers exchangeable

for goods and services for providing drug-free urine samples (Higgins et al., 1991). Voucher-based reinforcement can increase abstinence from a wide range of drugs (Lussier et al., 2006). The PI (Silverman) and others (Castells et al., 2009) have shown that voucher-based reinforcement can increase cocaine abstinence in injection drug users in methadone treatment (Silverman et al., 1996; 1998); and that high value vouchers can initiate abstinence in refractory injection drug users (Dallery et al., 2001; Silverman et al., 1999).

Abstinence reinforcement as maintenance intervention. As with other treatments, many patients relapse to drug use after abstinence reinforcement is discontinued. To address this, Silverman (PI) and colleagues have employed abstinence reinforcement as a maintenance intervention and showed that sustained voucher reinforcement could maintain cocaine abstinence for a year in injection drug users (Silverman et al., 2004).

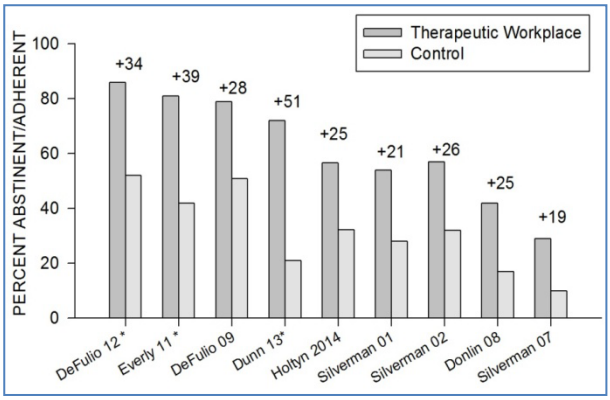
The Therapeutic Workplace to Address the Chronic Nature of Drug Addiction

The need for high magnitude and long duration abstinence reinforcement raises an obvious practical problem: How can high magnitude and long duration abstinence reinforcement be financed? Silverman and his colleagues developed the Therapeutic Workplace to provide a potential solution to this problem.

Employment-based reinforcement. The essential features of the intervention are simple: Participants are hired and paid to work, as in typical employment. To promote abstinence, participants must provide objective evidence of drug abstinence to maintain access to the workplace and maintain maximum pay. The approach is useful because it does not require an independent source of funds to address abstinence, but instead harnesses the reinforcing effects of employment-based wages to reinforce abstinence. Since employment can be sustained for years, this approach offers the potential advantage of maintaining high magnitude employment-based abstinence reinforcement over long periods of time.

Phases of treatment. The Therapeutic Workplace was designed to treat low-income, unemployed drug-dependent women. Since many women lacked job skills (Silverman et al., 1995), we designed two phases of treatment. During Phase 1, each patient's "job" was to participate in a stipend-supported training program designed to establish job skills and initiate abstinence. Once participants initiated abstinence and acquired skills, they progressed to Phase 2 and were hired as employees in a business and performed data entry jobs (Silverman et al., 2005). Employment-based abstinence reinforcement is maintained throughout both phases.

Therapeutic Workplace research. Our initial study showed that the Therapeutic Workplace could initiate (Silverman et al., 2001) and maintain heroin and cocaine abstinence for 3 years (Silverman et al., 2002) in pregnant and recently postpartum methadone patients. Other studies showed that employment-based abstinence reinforcement could increase cocaine abstinence in unemployed injection drug users (Silverman et al., 2007) and initiate (Donlin et al., 2008) and maintain (DeFulio et al., 2009) cocaine abstinence in welfare recipients who used cocaine during methadone treatment, as well as in out-of-treatment injection drug users (Holtyn et al., 2014). Three studies showed that the Therapeutic Workplace could promote adherence to naltrexone in opioid dependent adults (Defulio et al., 2012; Dunn et al., 2013; Everly et al., 2011). The adjacent figure shows outcomes from 9 studies evaluating the Therapeutic Workplace on cocaine abstinence and naltrexone adherence (asterisks). Values above the bars show the amount of increase produced by the Therapeutic Workplace; all were significant. See Silverman et al. (2012).



A critical challenge. One study described above showed that a year-long exposure to employment-based abstinence reinforcement during Phase 2 could sustain cocaine abstinence and prevent relapse throughout a year of employment (DeFulio et al., 2009). That study also showed that many participants relapsed to cocaine use during the follow-up year after the employment-based abstinence-reinforcement was discontinued (DeFulio & Silverman, 2011). Overall, our research shows that employment-based reinforcement can initiate and maintain cocaine abstinence; however, as with other treatments like methadone, our research also suggests it may be necessary to maintain the employment-based abstinence reinforcement contingencies over long periods of time and possibly indefinitely to prevent

relapse in some patients. Our next challenge is to develop cost-effective ways of arranging long-term exposure to employment-based abstinence reinforcement.

INNOVATION

Models to Arrange Long-Term Employment-Based Abstinence Reinforcement

We are developing three models to maintain employment-based abstinence reinforcement. Under all models, individuals enroll in Phase 1 of the Therapeutic Workplace to initiate abstinence and establish skills. The models differ in how employment-based reinforcement would be maintained over time.

The Social Business Model. Under the Social Business model, Phase 1 graduates are hired as employees in a social business. A social business, a concept that won Muhammad Yunus the Nobel Prize (http://www.nobelprize.org/nobel_prizes/peace/laureates/2006), is a business that exists to address the needs of a low-income population (Weber and Yunus 2010). The Therapeutic Workplace social business maintains employment and employment-based abstinence reinforcement. We established a Therapeutic Workplace social business, Hopkins Data Services, which provided data entry services to customers (Silverman et al., 2005; http://www.hopkinsmedicine.org/dome/0201/index.cfm). Our experience suggests that the Social Business model could be feasible (Silverman et al., 2005), but it may have limited capacities.

The Cooperative Employer Model. Under the Cooperative Employer model, a community employer hires graduates of Phase 1. The Cooperative Employer requires that employees undergo random drug testing and remain abstinent to maintain employment. We are testing this model (R34 DA032778). This model may provide added employment slots, but could have limited capacity, since it requires cooperating employers.

The Wage Supplement Model. Under the Wage Supplement Model, graduates of Phase 1 are offered abstinence-contingent wage supplements if they maintain competitive employment. Governments in Minnesota, Connecticut, Milwaukee, New York, and Canada have used wage supplements to increase employment in welfare recipients (Berlin, 2007; Michalopoulos, 2005; Riccio et al., 2010). This model harnesses the power of wage supplements to promote employment, while simultaneously using the wage supplements to reinforce drug abstinence. We have used abstinence-contingent wage supplements, but only to maintain abstinence in occasional participants who obtain employment while participating in the Therapeutic Workplace (e.g., Silverman et al., 2002). We have not yet systematically evaluated their effectiveness.

Development and Evaluation of the Abstinence-Contingent Wage Supplement Model

The Wage Supplement Model could expand the employment opportunities for Therapeutic Workplace participants and provide a financially beneficial means of arranging employment-based abstinence reinforcement as a long-term intervention. However, three critical challenges must be addressed: 1) we must incorporate a method to increase employment in Therapeutic Workplace participants; 2) we must evaluate the effectiveness of abstinence-contingent wage supplements in maintaining drug abstinence; and 3) we must assess the economic costs and benefits of abstinence-contingent wage supplements. We propose to evaluate the effectiveness and financial benefits of a novel Abstinence-Contingent Wage Supplement Model in promoting long-term employment and drug abstinence in injection drug users who use cocaine.

Individual Placement and Support (IPS) to increase employment. Increasing employment is critical both to reduce poverty and unemployment, risk factors for injection drug use and HIV; and to facilitate the success of the Therapeutic Workplace's Abstinence-Contingent Wage Supplement Model. Employment interventions for unemployed drug users have been consistently ineffective (Magura et al., 2004). Notably, a multi-site study by the NIDA Clinical Trials Network of the Job Seekers Workshop failed to show any effect of that intervention (Svikis et al., 2012). Therapeutic Workplace participants are employed at significantly higher rates after participation in the Therapeutic Workplace than before, but still only about 20% of participants work at fulltime after Therapeutic Workplace participation (Sigurdsson et al., 2011). To increase employment, we will combine the Therapeutic Workplace with the Individual Placement and Support (IPS) model of supported employment. IPS was designed to promote competitive employment in persons with severe mental illness. IPS is a common-sense employment intervention that involves rapid job search, promotes competitive employment, considers the participant's preferences, and provides job supports and benefits counseling. IPS is implemented by employment specialists who establish relationships with potential employers, and work with participants individually and in groups to identify available jobs, prepare applications, and to apply for positions. Employment specialists also provide support to participants during employment to increase success in a job. IPS is offered on a long-term

basis, with expectation that participants may need assistance repeatedly over time. IPS has been shown effective in increasing employment across many U.S. states, across several countries, and across a variety of economic conditions (Bond et al., 2012). A secondary analysis showed that IPS produced significant increases in employment in a subset of individuals who were dually diagnosed with severe mental illness and a substance use disorder (Mueser et al., 2011). We will adapt IPS to promote employment in participants after they initiate abstinence and acquire basic job skills in the Therapeutic Workplace. The developer of IPS (Drake), a co-investigator on this grant, will oversee IPS implementation. This study will be the first application of this proven employment intervention in low-income injection drug users.

Wage supplements to increase employment. Our research shows that participants will not attend our training program or work consistently on training without incentives (Silverman et al., 1996; Wong et al., 2004a,b; Koffarnus, Wong et al., 2013; Koffarnus, DeFulio et al., 2013). To increase motivation of participants to engage in IPS and obtain employment, participants will earn wage supplements for maintaining competitive employment. Wage supplements can promote employment in welfare recipients (Berlin, 2007; Michalopoulos, 2005; Riccio et al., 2010). Given the failure of employment interventions for unemployed drug users, combining IPS and wage supplements is warranted and could increase employment in this difficult population.

Abstinence contingency in provision of wage supplements to prevent relapse. Our research shows that employment alone is not sufficient to maintain abstinence. In the most relevant study (DeFulio et al., 2009), after completing Phase 1, participants who initiated cocaine abstinence were hired in our Phase 2 data entry business for one year and randomly assigned to two groups. Employment Only participants could work independent of their urinalysis results, like typical employment; Abstinence-Contingent Employment participants had to provide drug-free urine samples to work and maintain maximum pay. During Phase 2, Abstinence-Contingent Employment participants provided significantly more cocaine-negative samples than Employment Only participants (79.3% and 50.7%, respectively). Based on this study, we expect that many participants who become employed will relapse to cocaine use when employment-based abstinence reinforcement is discontinued. To sustain abstinence, participants who become employed will earn abstinence-contingent wage supplements as long as they continue to provide drug-free urine samples. If a participant obtains competitive employment, the participant will receive wage supplements ($8/hr) for verified employment. The maximum amount in wage supplements will be available as long as the participant continues to provide drug-free urine samples. To reduce the burden of providing urine samples, the probability of being required to provide urine samples will be gradually reduced over time, as we did previously (DeFulio et al., 2009).

Utilization of federal workplace drug testing infrastructure and practices. To facilitate ultimate dissemination of this intervention, we will use the existing Federal workplace drug testing infrastructure and practices to conduct drug testing during the employment phase of the intervention. An enormous infrastructure and rigorous guidelines for workplace drug testing exist that will be repurposed to apply employment-based abstinence reinforcement as a therapeutic intervention. The system is overseen by the U.S. Department of Transportation (DOT) and has been used to protect the public from the hazards associated with drug-impaired workers. Beyond this protective function, our research on employment-based abstinence reinforcement suggests that the Federal drug testing system could have considerable therapeutic benefits, and could be used for a wide range of individuals with drug problems beyond those in safety-sensitive jobs.

The DOT system utilizes over 10,000 SAMHSA certified collection facilities throughout the United States. Each collection facility collects the sample and sends it to a SAMHSA certified laboratory for testing. All collection sites use procedures that are in compliance with DOT regulations and are designed to ensure safe, secure, valid specimen collection (http://www.dot.gov/ost/dapc/index.html). Under DOT regulations, all positive drug tests must be reviewed by a Medical Review Officer (MRO; http://www.dot.gov/ost/dapc/mro.html) to ensure that all procedures were followed properly. Many specialized private companies manage workplace drug testing and related services for employers and so employers do not need to have expertise in addiction or workplace drug testing. Our system will be managed by one of those companies: American Substance Abuse Professionals (ASAP®), a leading provider of workplace substance abuse services in the U.S. (see https://go2asap.com/). When a participant in the abstinence-contingent wage supplement program becomes employed in a community job, a drug testing schedule will be established for the participant and this schedule will be shared with *ASAP®*. Participants will call the wage supplement staff in the morning of every Monday, Wednesday and Friday to see if they need to provide a urine sample that day. When required, the participant will report to our

urinalysis laboratory or one of the SAMHSA certified collection facilities in Baltimore. The urine samples will be tested for opiates and cocaine. If testing at a SAMHSA facility, the testing facility will send the results to ASAP® and to the wage supplement staff. The wage supplement staff will inform the participant of the results of the urine testing. If testing at a SAMHSA facility, positive tests will be reviewed by an MRO who will interview the participant to investigate any irregularities or employee concerns.

The cost-effectiveness and cost-benefit of abstinence-contingent wage supplements. We expect that abstinence-contingent wage supplements will be comparable in cost to buprenorphine maintenance (Schackman et al., 2012) and less expensive than extended-release naltrexone (Kennedy et al., 2011). We will assess the costs, cost-effectiveness and cost-benefits of IPS Plus Abstinence-Contingent Wage Supplements. Dunlap and Zarkin (Co-Investigators), experts in economic analyses, will conduct these analyses.

How Does Work Help Recovery? Clues from Ambulatory Monitoring

As we begin a new Therapeutic Workplace study, we have an opportunity to address questions about how people experience work during recovery from addiction. We intend to follow up on findings recently published by our colleagues at the NIDA IRP. Using data from the ambulatory-monitoring technique called ecological momentary assessment (EMA), they showed that methadone-maintained misusers of heroin and cocaine were less stressed, more happy, and less prone to cocaine craving when at their various workplaces than anywhere else (Epstein & Preston, 2012). Work accounted for 30% of the variance in happiness and 50% of the variance in cocaine craving. Mood improvements occurred specifically in the presence of coworkers (not other companions). This EMA finding, the opposite of what occurs in EMA studies of the general population, might mean that work was a respite from drug-using companions or from environmental stressors. We aim to replicate and extend this finding in the Therapeutic Workplace (which we have always noted, anecdotally, is well liked by our participants). We intend to use *geographical* momentary assessment (GMA), in which EMA is supplemented by geolocation tracking so mood and behavior can be assessed in terms of activity space and environmental exposures. Our NIDA IRP colleagues have been using GMA successfully in their outpatients (Epstein et al., 2014).

4. Study Procedures

Procedures for COVID-19

We will complete the remaining assessments without any in person contact. Interviews will be conducted over the phone and when possible we will obtain urine sample results from each participant's clinic. To do that, participants can ask their clinic to send us their urinalysis results. If needed, we will mail a re-loadable credit card to participants.

Recruitment Procedures

Identifying, Screening and Consenting Participants

Participants will be recruited from methadone and buprenorphine programs in Baltimore using procedures that we have used in prior evaluations of the Therapeutic Workplace (Donlin et al., 2008; Silverman et al., 2007). First, we will inform staff at methadone and buprenorphine treatment programs in Baltimore about the study and encourage them to refer potential participants to us. Second, we will post flyers and distribute business cards and information sheets with our toll-free number in each of these programs. Copies of the proposed flyer, business card and information sheets are enclosed with this application. Third, we will visit programs and recruit for the study onsite at each program. Fourth, as in our previous studies, participants will have the optional opportunity to earn incentives for referring people who are interested in the study. If a referral attends the initial screening appointment and completes the necessary assessments, the participant who referred the person will receive up to $20. If a referred person enrolls in the main study, the participant who referred the person will receive up to $40for making the referral.

Experimental Design and Groups

Phase 1 Abstinence Initiation and Job Skills Training

All participants will be invited to attend Phase 1 of the Therapeutic Workplace for about 3 months where they can earn up to about $40 every weekday and provide urine samples every Monday, Wednesday and Friday. To engage participants, both groups will be allowed to earn wages independent of their urinalysis results for the first 5 weeks.

Delayed Work vs. Immediate Work group. To assess the potential value of working in the workplace every weekday, upon enrollment in the study participants will be randomly assigned to a delayed work group or to an immediate work group. The delayed work participants will be paid a daily wage of $40 for coming to the workplace to sign in and provide a urine sample (on Mondays,

Wednesdays, and Fridays). The immediate work group will be invited to work in the workplace 4 hrs every weekday, where they can earn about $10/hr for participating in our job skills training program. This initial period will last for 3 weeks. After the initial three weeks, all participants will be invited to work in the workplace for 4 hours every weekday. GMA data (see below) will be used to compare participants' mood and behavior during weeks that they are at work (Immediate Work group) to weeks where they are not at work (Delayed Work group).

Abstinence initiation. After the 5 week induction period, participants will be required to provide urine samples negative for opiates and cocaine to maintain maximum pay. To allow us to evaluate the effectiveness of the contingencies for opiate and cocaine abstinence in promoting abstinence, we will implement the requirement for opiate-negative and cocaine-negative urine samples after varying durations in the induction period. At the end of Phase 1, participants will be randomly assigned to the study groups.

*Vacation days***.** On quasi-randomly selected work days, all participants will have a paid "vacation" day. During a vacation day, participants will be able to earn their typical pay, but they will not have to attend the workplace and work to earn it. This will enable us to assess how unexpected free time affects mood and behavior. We have used similar paid vacation days to maintain participants' pay during actual holidays, weather emergences and other workplace closings. GMA data (see below) will be used to compare participants' mood and behavior on days that they are at work (regular work days) to days where they are not at work (vacation days)

Geographical Momentary Assessment (GMA). The GMA-related procedures will occur for 12 weeks of the first 3 months of Phase 1. One week after signing informed consent, all participants will be issued a smartphone for GMA. The one-week delay is to help ensure that smartphones are issued only to participants who intend to return.

For ambulatory assessment of mood and behavior, questions will be programmed as an application on the smartphone. The smartphone's integrated GPS unit will collect geographical location data at 5-minute intervals. The app will be password protected on the phone; questionnaire responses and GPS data will be encrypted and transmitted from the smartphone to a secure NIH server. Participants will be able to use the phones for their personal use. In addition to GMA data for location and self-report, we will record the amount of time and frequency of phone use (voice and text messaging), but no text or voice content will be recorded.

When the smartphones are issued, participants will be shown how to use and charge them, and will be asked to carry them at all times. At each visit to the Therapeutic Workplace, their possession and the charge level of the phone will be recorded. The smartphones will be activated for airtime for collection of location (GPS) and real-time self-report data and for personal use as a mobile phone by the participant. The visit for initial training on the smartphone is expected to take 30 minutes, during which participants will also complete the Perceived Neighborhood Scale (Martinez et al., 2002), which is a questionnaire that will help us understand their interactions with their home environments.

Participants will carry the smartphones for up to 12 weeks, during which they will make four types of entries. Each entry takes 3-5 minutes. The list of questions presented at each type of entry is provided in the Supplemental Documents section of the e-IRB application.

- Random-prompt entries: Participants will be prompted three times per day by the app, at random times during their waking hours. They will report their mood, stress level, environmental setting, activities, and degree of craving. Hours for prompting will be adjustable in accordance with the participant's typical sleep/wake schedule; participants will also be able to turn off random prompting in settings where it would be disruptive (such as driving, showering, or religious services).
- Drug-use entries: Participants will initiate an entry whenever they use cocaine, heroin, another opioid or stimulant outside of a medical context.
- Drug-craving entries: Participants will initiate an entry whenever they crave cocaine, heroin or another opioid, without using.
- Stress-event entries: Participants will initiate an entry whenever they feel overwhelmed, anxious, or stressed more than usual.
- Cue-exposure entries: Participants will make a brief entry (one question) each time they see something that makes them think about cocaine.

Once a week, participants will meet with a study staff member to review the participant's compliance with GMA entries and compare their drug-use entries with the results of the urine drug screens conducted three times per week. Compensation for the GMA portion of the study will be based on the

correspondence between urine and self-report for each 7-day period. We will use the payment schedule described below to reinforce use and maintenance of the phone, self-reports of drug use, and compliance with EMA prompts.

Participants' willingness to carry the smartphone and provide GMA data is crucial to this aspect of the study. At study intake, and again during GMA training, we will attempt to give participants a sense of their opportunity to "make their voices heard" by confirming or refuting researchers' assumptions about work and leisure time during recovery from addiction.

Care will also be taken to allay participant concerns about the clinical consequences of providing GMA data. At study intake, and again during GMA training, participants will be assured that the details of their GMA data will be seen only by the investigators; no information will be conveyed to their methadone treatment programs. The questionnaires on the smartphones will require a password to display, and a demo (assessing innocuous items, not drug-related) will be available on the phone if the participant wants to demonstrate the app to someone else.

Participants will be expected to carry their smartphones whenever they leave home and to charge them as necessary. Each day that the participant comes to the Therapeutic Workplace, we will check that they have the phone and that it is working and charged. Participants will receive a weekly bonus of $5 if they bring the charged phone to the Therapeutic Workplace each day. Participants will earn $30/week if they respond to at least 82% of all cumulative random prompts within 15 minutes. To ensure compliance with drug use reports, participants may earn up to $15/week ($5 for each time their urine drug screen matches their self-reported drug use entries). Compliance will be assessed each week prior to payment. At the end of month 3, participants will return the smartphone to the investigators; they may choose to keep their smartphone or return them for $200.

Participants may be dropped from the GMA portion of the study, and airtime on the phone access will be terminated, if they do not meet compliance goals or they lose or damage their smartphone. Being dropped from the GMA portion will not affect their participation in the main study. Criteria for being dropped are:

- Fail to bring the smartphone in, or to maintain its charge, on 12 occasions over 12 weeks.
- Participant will receive approximately 252 prompts over 12 weeks, approximately 21 per week. If a participant fails to respond to more than 16 (76%) of total possible prompts in a given week, the participant will be reminded of the requirement; if the participant's failure rate remains above 25% for a second consecutive week, the participant will be discharged dropped from the GMA study; this will not affect their participation in the main study.
- Lose or damage their smartphone. ("Damage" is defined as anything that renders the smartphone permanently unusable for study purposes.)

Quality of Life Monitoring. Quality of life, which encompasses an individual's satisfaction with life in general, has been proposed as an outcome measure and an important target in substance-abuse treatment studies. About one week after participants receive their study-provided smartphone, they may be provided with access to an application on their smartphones called "Delight Me." We will use the Delight Me platform to monitor quality of life during Phase 1 of the current study. We will administer questions to participants through the Delight Me application that will ask them to make a subjective evaluation of their lives in specific domains (e.g., health, social support, recreation). The questions will be available to answer on either a daily or a weekly basis, depending on the question. The questions we will use are uploaded under the Supplemental Documents section of the e-IRB application. Participants' responses to these questions will be stored in a secure database that restricts access and uses encryption while at rest. These data also will be protected while in transit between any device used to access Delight Me and the secure database. Only approved research staff will be able to access participants' responses to the questions administered in Delight Me. Participants will be able to earn up to $10 per week over 11 weeks for answering questions in the Delight Me application. We will evaluate how much participants use the Delight Me platform, whether participants' responses to the questions change over time, and if these changes relate to drug use or measures of workplace attendance during Phase 1.

HIV education. Since participants in this study are at substantial risk for HIV, they may be taught about the benefits of HIV preventative behaviors, pre-exposure prophylaxis (PrEP) medical care, and PrEP adherence. The Centers for Disease Control and Prevention has suggested that injection drug users who are at substantial risk for HIV should take PrEP medication to reduce the chance that they will acquire HIV. Participants will be able to earn incentives for engaging in this education. Participants will be able to earn up to about $10/hour for participating in our health education program, part of which will be based on

performance on the training program. Some or all of the training may be given through a computer-based training program. We may also evaluate the effectiveness of the education program by giving participants tests before and after participants complete a portion of or the entire training program.

We may also administer a questionnaire to determine who is appropriate for PrEP medical care. The questionnaire is uploaded under the Supplemental Documents section of the e-IRB application. We may also refer appropriate participants to receive PrEP medical care and follow-up to determine if they enroll in that care.

Bull's Eye Game. Participants may work on a computer-based assessment called the Bull's Eye Game. The Bull's Eye Game is designed to assess participants' temporal learning (e.g., learning about the time to reward availability) and cue sensitivity (e.g., understanding how other stimuli in the environment predict rewards). Each session will consist of regular trials and test trials. During regular trials, a Bull's Eye target will appear on the computer screen. The target will move across the screen at different speeds. Participants can press a key on the keyboard to hit the center of the screen. Participants will earn points if they press the key when any part of the target is at the center of the screen. Participants will lose points if they press the key when the target is not in the center of the screen. In occasional test trials, participants will not be able to see the target. During these test trials, participants will guess when they can earn points. Participants will earn and lose points in regular and test trials according to the same rules. In most conditions, other visual cues (e.g., the background color of the screen) will predict the time to point availability. Sometimes those visual cues will be reliable predictors of point availability and sometimes they will miscue targets. Across conditions, we will be able to assess how well participants learn the time to point availability and how participants ignore or attend to other aspects of the learning environment (e.g., visual cues and miscues) through their response patterns in test trials. This information will provide some insight into fundamental learning processes in adults with histories of substance abuse. As in other programs, participants will be able to earn approximately $10/hour for participating in this program, part of which will be based on the number of points they earn on the task.

Academic and computer skills training. As described below (see Benefits), participants may have access to training in typing, keypad, general computer use, reading, spelling, math, GED preparation, and the use of Microsoft computer applications. We may evaluate the effectiveness of the academic and computer skills training programs by giving participants tests, such as the Wide Range Achievement Test, before and after participants complete a portion of or the entire training program.

Review and expungement of criminal record. Criminal records are a major barrier to competitive employment in adults with a history of illicit drug use. To help participants prepare for competitive employment, we may collaborate with community partners (e.g., Maryland Legal Aid) who offer free legal assistance to participants in Phases 1 and 2. This assistance typically consists of determining eligibility for expungement, processing petitions for expungement of criminal records, and other free services approved by the legal team. Participants are notified by research staff that legal assistance is available, and that participation is voluntary. We may collect data to describe and evaluate the expungement process so we may better understand legal barriers to employment in adults with a history of illicit drug use. The data we would collect are the types of offenses participants have on their public records (i.e., records available to potential future employers), the number of convictions on record, which records are eligible or ineligible for expungement, whether petitions for expungement are filed by the legal team, whether petitions for expungement are granted or require a hearing, and how long it takes for participants to have their records expunged. We may publish an article to describe the expungement process and de-identified data of our participants. All data that we collect and publish on the criminal histories of our participants will be data that are publicly available.

Random Assignment

Participants (N = 120) will be randomly assigned to an IPS Only (Control) or IPS Plus Abstinence-Contingent Wage Supplements group. A computerized urn randomization procedure (Wei & Lachin, 1988) will be used to balance groups on three baseline characteristics that may influence outcome: (1) percentage of the three monthly urine samples collected prior to random assignment that are positive for cocaine (≥ rolling median, Y/N); (2) percentage of the three monthly urine samples collected prior to random assignment that are positive for opiates (≥ rolling median, Y/N); and (3) completed high school or obtained a GED (Yes/No). Participants will be stratified by cocaine and opiate use because drug use at random assignment should predict abstinence from opiates and cocaine and possibly employment during the intervention evaluation period. High school completion or GED should be associated with employment

during the intervention evaluation period. This number of stratification variables has been sufficient to balance groups in past studies.

Individual Placement and Support (IPS) & Abstinence-Contingent Wage Supplement Group

This study will evaluate a novel intervention designed to promote long term employment and drug abstinence. The intervention will combine Individual Placement and Support with abstinence-contingent wage supplements. This group will receive the full intervention being evaluated in this study for one year.

Individual Placement and Support (IPS). To increase employment, after completing Phase 1 of the Therapeutic Workplace, participants will be offered Individual Placement and Support (IPS) model of supported employment for one year. IPS involves rapid job search, promotes competitive employment, considers the participant's preferences, and provides job supports and benefits counseling. The employment specialist will establish relationships will potential employers and work with participants to identify potential jobs, prepare applications, and to apply for positions. The employment specialist will provide IPS under the supervision of Robert Drake (Co-I), the developer of IPS, and Lawrence Abramson (Consultant).

Fidelity measures will be collected to ensure that IPS is followed consistently. Using the procedures outlined by Bond, Peterson, Becker and Drake (2012), two trained IPS assessors will visit our research unit for 1.5 days per year and use IPS-25 to assess IPS fidelity. IPS-25 consists of 25 items that specify critical features of IPS. Each item is rated on a 5-point scale which represents the degree to which the program adheres to that feature of IPS. The assessors will interview our staff and our employment specialist, observe team meetings and community contacts with employers, interview clients, and review client charts. After the site visit, the assessors will independently make fidelity ratings and then reconcile discrepancies. The assessors will also prepare a fidelity report and provide recommendations for improvement. IPS-25 fidelity scores have been shown to be significantly associated with rates of employment (Bond et al., 2012). This fidelity assessment process has led to programs attaining good fidelity across hundreds of implementations.

Abstinence-contingent wage supplements. Participants in this group will receive abstinence-contingent wage supplements. Abstinence-contingent wage supplements should have three main effects: 1) promote engagement in IPS, 2) promote competitive employment, and 3) maintain drug abstinence. Before obtaining competitive employment, participants will be able to earn wage supplements for attending IPS sessions each week, and for completing specific tasks prescribed by IPS including developing a worker profile, applying for appropriate jobs, and completing job interviews. This incentive system will be designed to allow participants to earn about $200 per week and will include methods to verify the completion of the target behaviors. If needed, we may offer bonus incentives to increase some job-seeking behaviors (e.g., completing job applications). We may also evaluate the effectiveness of those bonus incentives, for example, by applying and withdrawing them to see if those bonus incentives are needed to promote the job seeking behaviors. Once a participant becomes employed, participants will be able to earn up to $8 per hour for every hour worked in a competitive job up to 40 hours per week verified by pay stubs. To maintain long-term abstinence from opiates and cocaine, participants will be required to provide urine samples to earn the maximum in wage supplements.

Abstinence monitoring. After random assignment, a drug testing schedule will be established for each participant and this schedule will be shared with *ASAP*®. Participants will be required to call our wage supplement staff every Monday, Wednesday and Friday morning to find out if they are required to report to our urinalysis laboratory or a participating SAMSHA-approved urine collection facility to provide a urine sample. Participants will be given a list of the participating collection facilities in the Baltimore area. One of the facilities is open 24 hours per day, 7 days per week; one is open from 7 am to 7 pm every weekday; one is open from 8 am to 8 pm every weekday; and one is open 8 am to 5 pm every weekday. If a participant is out of town (e.g., on vacation), the participant can contact our laboratory staff, who will identify the nearest collection facility for that participant by conducting a geo-access match using the zip codes and physical address of the participant's location. The results of testing will be available to the wage supplement staff on a secure website.

Resetting the wage supplement value. Participants will continue to be eligible to earn the maximum in abstinence-contingent wage supplement as long as they continue to provide opiate- and cocaine-negative urine samples on all required sample collection days. If a participant ever fails to provide a scheduled sample or provides a urine sample that is positive for opiates or cocaine, the value of the wage supplement will be reduced to $1.00 per hour and the frequency of required urine collections will be increased to the initial frequency of two days per week on average. The value of the wage supplement will

be increased by $1.00 per hour for every day that the participants provide a drug negative sample. In addition, the probability of required urine sample collections will be gradually decreased again as long as the participant continues to provide drug-negative urine samples on required urine collection days. By the end of the year, participants should be required to provide urine samples on one randomly selected Monday, Wednesday or Friday every two weeks.

Individual Placement and Support (IPS) Only Group

Participants assigned to the Individual Placement and Support (IPS) Only group will receive the IPS intervention as described above. This group will receive IPS as it has been implemented thus far for people with severe mental illness. Participants in this group will not receive the monetary incentive for performing IPS tasks or maintaining competitive employment (wage supplement).

Intake, Outcome & Economic Assessments

For the primary aim of the study, assessments will be conducted at intake, every 30 days throughout the 3-month abstinence initiation period, every 30 days throughout the 12-month intervention evaluation period after random assignment and then at 3, 6, 9 and 12 months after the end of the intervention evaluation period. Assessments will be administered using Qualtrics, a web-based software (http://qualtrics.com/) to administer and record responses for the questionnaires administered that we are using in our other protocols. If the Qualtrics is not available, we may administer assessments using paper forms. The paper versions of the assessments are included in the section 19 for Supplemental Study Documents. Urine samples will be collected at each of these time points and we may test for cocaine, opiates, marijuana, amphetamines, methamphetamines, methadone, buprenorphine, barbiturates, benzodiazepines, MDMA, PCP, and oxycodone.

To gain verified and objective records of employment, we may get an objective measure of each participant's employment history by getting each participant's earnings history using federal Form SSA-7050-F4 (10-2016) UF, REQUEST FOR SOCIAL SECURITY EARNINGS INFORMATION. Participants and research staff will complete this form and have the participant's earnings history sent to our research unit. Our research unit will pay for the costs of this service. We may request these documents one or more times. We will take the following steps to protect this sensitive information in our study databases (see also Section 8b): (1) when storing a completed form, we will redact name, date of birth, and social security number from the written document and label the document with an ID number; (2) keep paper copies in a locked file cabinet in a locked office and never keep documents out while unattended by research staff; (3) only enter relevant information into the database (i.e., information about when participants worked, how much they earned, and what type of employment they had); and (4) maintain a confidentiality certificate from the NIH. The risks associated with collecting this information are explained on the consent form.

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

Participants will be invited to attend Phase 1 of the therapeutic workplace every weekday for 3 months. Participants in the immediate-work group will attend for 4 hours every weekday. Participants in the delayed work group will be asked to come to the workplace every day for a brief visit (30 minutes or less) to complete study measures for the first 3 weeks and then for the full 4 hours for the remainder of the 3 month period of Phase 1. All participants that report to be assessed at the end of Phase 1 will be randomly assigned to the primary study groups and offered Individual Placement and Support for 1 year. The IPS intervention is designed to promote employment in competitive community workplaces. All participants will be invited to participate in an intake assessment to determine eligibility and characterize the population. Outcome assessments will be conducted every 30 days throughout the 3-month abstinence initiation period, every 30 days throughout the 12-month intervention evaluation period after random assignment, and then at 3, 6, 9 and 12 months after the end of the intervention evaluation period.

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

NA

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

NA

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

NA

e. Definition of treatment failure or participant removal criteria.

Participants will be removed from the study if they threaten the safety of CLH staff or other research participants, or of any other persons on the Johns Hopkins Bayview Campus.

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

Throughout the study, participants will be given referrals to services they might need (e.g., drug counseling, housing, medical, or employment services).

5. Inclusion/Exclusion Criteria

Inclusion criteria: a) ≥18 yrs old; b) unemployed; c) provide an opioid-positive (methadone, buprenorphine, or morphine) urine sample at intake;; e) in methadone or buprenorphine treatment or meet DSM criteria for heroin dependence; and g) express interest in obtaining competitive employment.

Exclusion criteria: a) report current suicidal/homicidal ideation; b) have a severe psychiatric disorder.

6. Drugs/ Substances/ Devices

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

NA

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

NA

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

NA

7. Study Statistics

We will compare the *IPS* Plus Abstinence-Contingent Wage Supplement and IPS Only participants on primary, secondary and economic measures. Each measure is associated with a *Specific Aim*.

a. Primary outcome variable.

Specific Aim. Assess the effectiveness of the IPS Plus Abstinence-Contingent Wage Supplements in preventing relapse to heroin and cocaine. We will assess rate of urine samples negative for opiates and cocaine at the 12 monthly assessments during the year after random assignment (Y/N at each assessment).

Specific Aim. Assess the effectiveness of the IPS Plus Abstinence-Contingent Wage Supplements in promoting employment. We will assess rate that participants report being employed at the 12 monthly assessments during the year after random assignment (Y/N at each assessment).

b. Secondary outcome variables.

Specific Aim. Assess the effectiveness of the IPS Plus Abstinence-Contingent Wage Supplements in reducing injection drug use. We will assess the rate that participants report injecting drugs in the past 30 days at the 12 monthly assessments in the year after random assignment (Y/N at each assessment).

Specific Aim. Assess the effectiveness of the IPS Plus Abstinence-Contingent Wage Supplements in reducing drug-related HIV risk behaviors. We will assess the rate that participants report sharing injection equipment (needles/syringes without disinfecting, cookers/cottons/rinse water, or drug solution) or trading unprotected sex for drugs or money in the past 30 days at the 12 monthly assessment during the year after random assignment (Y/N at each assessment). If the IPS Plus Abstinence-Contingent Wage Supplements reduces cocaine and opiate use, it should reduce these risk behaviors.

Specific Aim. Assess the effectiveness of the IPS Plus Abstinence-Contingent Wage Supplements in reducing family poverty. We will assess whether family income is at or below the federal poverty level at the 12 monthly assessments during the year after random assignment (Y/N at each assessment) with and without wage supplement earnings. IPS Plus Abstinence-Contingent Wage Supplements should reduce poverty.

Specific Aim. Assess the effectives of the IPS Plus Abstinence-Contingent Wage Supplements in promoting long-term drug abstinence and employment and in reducing HIV risk. We will compare the groups on all measures of heroin and cocaine use, employment, and HIV risk behaviors at 3-, 6-, 9- and 12-month follow-up assessment time points after IPS and abstinence-contingent wage supplements have ended.

Specific Aim. Assess the costs of treatment for IPS Only and IPS Plus Abstinence-Contingent Wage Supplements. We will assess the total cost per participant of both study interventions. We expect that treatment costs for IPS Plus Abstinence-Contingent Wage Supplements will be higher per person relative to the IPS Only due to the wage supplements and because we expect that IPS Plus Abstinence-Wage Supplement participants will have greater treatment engagement.

Specific Aim. Assess the cost-effectiveness of IPS Plus Abstinence-Contingent Wage Supplements. Separate cost-effectiveness analyses will be conducted for the outcomes of substance use, employment, and drug-related HIV risk behavior. We will assess incremental cost-effectiveness ratio (ICER) by dividing the difference in costs of two interventions by the difference in the effects of the two interventions. The estimated ICER can be interpreted as dollars spent per unit of desired outcomes gained. We expect that IPS Plus Abstinence-Contingent Wage Supplements will yield better ICERs for all three measures.

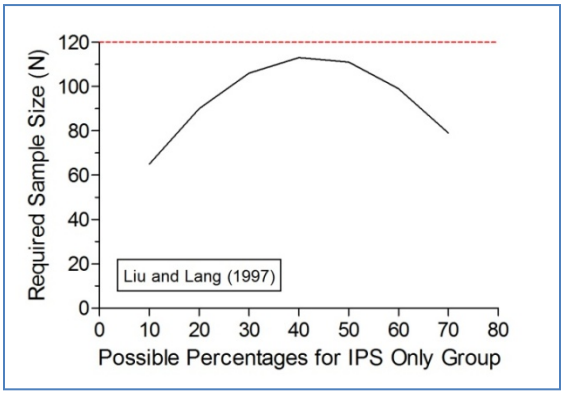
Specific Aim. Assess the cost-benefit of IPS Plus Abstinence-Contingent Wage Supplements. We will perform a Cost-Benefit Analysis (CBA) to examine the monetized benefits relative to costs for the two intervention conditions. The economic outcomes are employment, crime, and health care utilization. We expect that IPS plus Wage Supplement will yield greater economic benefits in criminal activity, health care utilization, and employment in the 24-month post enrollment time period relative to its costs than the IPS only condition.

Specific Aim. Geographical Momentary Assessment. We will assess collect the four types of ambulatory entries described above (randomly prompted entries and three types of event-related entries), along with time-stamped latitude and longitude data from the smartphone's GPS unit. In some analyses, we will examine the latitude and longitude data in terms of objective information about social disorder in the neighborhoods where they were collected, as we have done in our published work (Epstein et al., 2014).

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

Power Analysis

The primary outcome measures will be analyzed with a longitudinal logistic regression model using GEE (Diggle et al., 2002). We used Liu and Liang (1997) to determine the total N required to detect differences between groups with 80% power. The adjacent figure shows the total number of participants (N) that would be required to detect a difference of 15% between the IPS Only and the IPS Plus Abstinent-Contingent Wage Supplement with the 12 monthly assessments. The adjacent figure shows possible percentages for the IPS Only group because that value affects the sample size required. Fifteen percent is smaller than any difference in any Therapeutic Workplace study in which we promoted cocaine abstinence in methadone patients. This difference is also smaller than any difference between Control and IPS groups in the percentage of participants that become employed. Based on this, we need a maximum of 120 participants (horizontal dashed line) to detect a difference between the IPS Only and the IPS Plus Abstinent-Contingent Wage Supplement groups of 15% or more on each primary outcome.



Statistical Analyses

Main analysis. All measures assessed repeatedly over time will be analyzed with a longitudinal logistic regression model. Within-person correlated outcomes will be handled using generalized estimating equations (GEE; Zeger et al., 1988). Measures assessed once will be analyzed using logistic regression. The magnitude of effect for both logistic regression and GEE will be expressed using odds ratios with 95% CI. Analyses will include all randomized participants as intent-to-treat, and will be adjusted for pre-specified covariates used for stratification (Pocock et al., 2002). Tests will be two-sided and p-values <.05 will be considered significant.

Moderator analyses. We will conduct analyses to identify variables that moderate the outcomes of our two primary outcome measures, employment and drug (opiates and cocaine) abstinence. We will examine differences in efficacy as a function of two variables assessed prior to random assignment by including interaction terms in our regression models: 1) Percentage of urine samples negative for opiates and cocaine at the three monthly urine samples collected prior to random assignment. 2) Completed high

school or obtained a GED (Y/N)? We expect that opiate and cocaine use prior to random assignment will be associated with higher rates of drug use and lower rates of employment during the year after random assignment. We expect that high school completion or obtaining a GED will be associated with higher rates of employment. We also expect that the effect of IPS Plus Abstinence-Contingent Wage Supplements will be affected by these variables.

We will conduct similar analyses to identify variables that moderate outcomes on employment and drug use during the follow-up year after IPS and abstinence-contingent wage supplements have ended. We will examine differences in outcomes during the follow-up year as a function of two variables assessed at the end of the intervention evaluation period by including interaction terms in our regression models: 1) Percentage of urine samples positive for cocaine or opiates at the last three monthly urine samples collected under the study interventions; 2) Highest hourly wage that each participant earned during the year after random assignment. We expect that opiate and cocaine use during the last 3 months under the study interventions will be associated with higher rates of drug use and lower rates of employment during the follow-up year. We expect that the highest wage achieved during the year that the study interventions were in effect will be associated with higher rates of employment and lower rates of drug use during the follow-up year. We also expect that IPS Plus Abstinence-Contingent Wage Supplements effects will be affected by these variables.

Missing data. We expect to collect >90% of assessments (see below). Our primary approach to handle missing data will be to impute all missing values as the adverse outcome (e.g., cocaine positive). Model parameter estimates from this approach will be compared to a method without imputation. If these methods yield differing results, conclusions will need to be tentative. To investigate sensitivity to missing values, participants with and without missing values will be compared by covariates and treatment assignment.

Analyses for the secondary GMA aim. Most of these analyses will be done by Dr. Preston's group. Like the other repeated measures, the GMA data will be analyzed with longitudinal regression models. Dr. Preston's group uses mixed models (Proc Mixed and Proc Glimmix in SAS 9.4) to handle within-person correlation and missing data. Tests will be two-sided and p-values <.05 will be considered significant. The main comparisons of interest will be: (a) Between-group comparisons of mood, craving, stress, and other GMA measures during weeks 2-3, when participants have been randomized to immediate versus the delayed work condition. (Waitlist participants who have other employment during weeks 2-3 will be excluded from most of these analyses.) (b) Within-person assessment of changes in those variables in the delayed work group, comparing weeks 2-3 to weeks 5-13. (c) Contrasts in all participants between unannounced vacation days and the corresponding weekdays from a week with no vacation. For comparisons a, b, and c, effect sizes are expected to be fairly large, because work accounted for 20-50% of the variance in mood and craving in a EMA prior study at the NIDA IRP (Epstein and Preston, 2012). We will also assess (d) between-group and within-person differences in GPS-assessed activity space during working and nonworking periods. We have no prior data on that question; those analyses will be exploratory.

Economic Analyses

Our economic evaluation will be done from the provider perspective.

Cost Analysis. We will derive cost estimates of intervention activities following an activity-based approach (Drummond et al., 2005; Gold et al., 1996; Zarkin, Dunlap et al., 2004; Zarkin et al., 2005; Zarkin, Dunlap, et al., 2008). The total cost per participant of each intervention condition will be the sum of (1) staff labor costs, (2) costs of building space, (3) costs of the wage supplements; and (4) costs of supplies or materials. The total intervention cost for each participant is the cost per activity multiplied by the number of activities or services received by the participant. Taking the mean across participants in an intervention condition yields the mean per participant cost of that intervention. We will collect data on the costs of the addiction treatment services because the IPS plus Abstinence-Contingent Wage Supplement condition may increase treatment attendance/retention which will affect the overall per-participant costs associated with the intervention. Treatment attendance will be captured in the modified Economic Form 90 AIR/ED. Standard addiction treatment costs will be drawn from the literature (e.g., Zarkin et al., 2004; Roebuck et al., 2003).

Cost-Effectiveness. Our Cost-Effectiveness Analysis (CEA) methodology (e.g., Zarkin et al.,1996, 1997, 2008; Dunlap et al., 2010) will combine the cost estimates described above with associated intervention effectiveness measures. Separate cost-effectiveness analyses will be conducted for substance use, employment, and drug-related HIV risk behavior. The incremental cost-effectiveness ratio (ICER) is calculated by dividing the difference in costs of two alternatives by the difference in effects of the

alternatives. The estimated ICER can be interpreted as dollars spent per unit of desired outcomes gained (e.g., $300 per day abstinent). To gauge ICER sampling uncertainty, we will calculate the CI via nonparametric bootstrap methods (Indurkhya et al., 2001; Briggs et al., 2006). We will also estimate cost-effectiveness acceptability curves (CEAC) using nonparametric bootstrap methods (e.g., Dunlap, et al., 2010; Zarkin et al., 2008; UKATT Research Team, 2005). The CEACs incorporate the inherent variability of cost and effectiveness estimates and show the probability that a treatment is cost-effective as a function of the policy maker's intrinsic valuation/willingness to pay for the clinical outcome.

Cost-Benefit. We will perform a Cost-Benefit Analysis to examine the monetized benefits relative to costs for the two intervention conditions. The key economic outcomes are employment, crime, and health care utilization. These outcomes will be assessed through the modified Economic Form 90 AIR/ED. The unit costs to be used in monetizing these economic outcomes will be drawn from various literature and public data sources (e.g., Zarkin et al, 2010; French et al. 1996; Roman et al., 1998; Cohen et al., 1994).

Sensitivity Analysis. We will conduct sensitivity analyses to assess whether the economic results are affected by changes in model parameters, such as assumptions made in estimating costs. We will perform one-way sensitivity analyses in which we examine the effect of changing one of the model parameters while holding all other parameters constant. We will also perform *n*-way sensitivity analyses in which *n* parameters of the model are varied jointly, holding all other parameters constant.

d. Early stopping rules.

The PI (K. Silverman, Ph.D.) and two co-investigators at Johns Hopkins University School of Medicine (A. Holtyn, Ph.D. and M. Fingerhood, M.D.) and one investigator who is not associated with the project (George E. Bigelow, Ph.D.) will provide data safety monitoring of the proposed trial. Reporting adverse events to the IRB and to NIH will be based on the guidelines of the Johns Hopkins Medicine Institutional Review Board (JHM IRB). To monitor adverse events, all staff members who have regular contact with study participants are instructed on the need to report to an investigator and the study monitor any indication that an adverse event has occurred. When the staff members and investigators learn of an adverse event, they will investigate until they have determined as many of the relevant details of the adverse event as possible, and an IRB adverse event form will be completed. To provide consistent monitoring of adverse events across groups, participants will be asked about all categories of adverse events at each routine assessment visit conducted throughout the study. The PI and the other investigators will review severe reports. At least one investigator will review each adverse event as it occurs. Staff will make summaries of the types of adverse events by study condition and add each new adverse event to that table. The investigators will review the table periodically and at the time of the annual reports to NIDA and the IRB. This frequency of review will be increased if the rate of adverse events occurs at a higher rate than anticipated. The protocol can be stopped based on recommendations of the investigators who are reviewing the adverse events in the study. We will ask the investigators to recommend that the trial be stopped if a review of the adverse events suggests to any of the investigators that the number of related adverse events is unacceptably high. The investigators will be allowed to request statistical analyses to compare the groups on the rates of different adverse events or to have the adverse event data summarized in other ways that they deem appropriate.

8. Risks

a. Medical risks

There is essentially no risk above those of normal daily living associated with the training or work in the Therapeutic Workplace, with participation in the Individual Placement and Support program, with obtaining employment in community workplaces, with the incentive program, or with the data collection procedures used in these studies.

b. Steps taken to minimize the risks.

To protect confidentiality, all research participants are identified by participant identification codes (Participant IDs) consisting of their initials and sequentially-assigned participant numbers on most forms and data files, and not by their names. Picture ID cards are maintained by staff in a locked container, and kept in a locked, secured area when not in use. All research data are stored in locked areas accessible only to research staff and are not left unattended. Documents with confidential information are shredded before being discarded. Confidential information is never given to anyone outside of the research program without the explicit written permission of the research participant. Only selected designated staff members are approved to give confidential information out after obtaining explicit written permission from the

participant. All research staff are trained in these procedures. We collect only general information about participant activities, legal and illegal. We do not collect information about specific illegal acts unless they are publicly available. In addition to these procedures, all outside persons who visit or work at the Center for Learning and Heatlh are required to sign a confidentiality agreement, in which they agree not to disclose any confidential information that they may become aware of in the course of their time at the center. All participants are also invited to take a break and leave the workplace when visitors come to the Center for Learning and Health. To further protect confidentiality, we will obtain a confidentiality certificate from NIH to protect data collected in this study. Finally, to protect the confidentiality of participants who become employed in a community job, we will not interact with an employer unless the participant gives explicit written permission.

c. Plan for reporting unanticipated problems or study deviations.

Unanticipated problems or study deviations will be reported based on the guidelines of the Johns Hopkins University School of Medicine IRB. Although JHU requires that incarcerations be reported to the IRB promptly, since our population is incarcerated frequently throughout our studies, we will report incarcerations at the annual renewal reports.

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

There are risks that the confidential information we collect could be revealed to people not involved in the research such as a friend, relative, or an outside organization. This could be embarrassing to the participant if the participant wanted to keep participation in the study secret. The legal risks are limited because we collect only general information about participant activities, legal and illegal. We do not collect information about specific illegal acts that are not publicly available. Thus, the risks associated with the assessments are not greater than the risks associated with routine psychological examinations or tests.

Risks associated with GMA data collection: Carrying the smartphones may be a burden to participants; we reduce this burden by providing carrying cases with belt clips. There is a risk of loss of confidentiality associated with carrying information on drug use and location; this risk will be minimized as the smartphones will have only coded identification numbers on them and will be password-protected. Carrying a smartphone may increase the likelihood of being robbed; however, as the use of such phones is becoming almost ubiquitous (even in low-SES populations), it is not likely that the risk of robbery is substantially increased over the usual risks. Dr. Preston and her colleagues have issued smartphones or PDAs to nearly 300 participants in prior studies without having encountered this problem. Similarly, all cellphones in the state of Maryland are now required to have position-tracking devices; therefore, any additional risk from location tracking by a GPS unit represents only a small increase over that of using a standard cellphone. Again, all information we collect will be protected under an NIH-issued Certificate of Confidentiality.

e. Financial risks to the participants.

There are no financial risks above those of normal daily living. Each participant is responsible for ensuring that the earning of incentives is reported properly to relevant government or private agencies and for determining whether or not the earning of vouchers will affect any benefits they might receive from those agencies.

9. Benefits

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

Benefits to human subjects. All participants will have access to training in skills that could be useful in obtaining employment. Training may be provided in typing, keypad, general computer use, reading, math, GED preparation, the use of Microsoft computer applications. IPS supported employment will be provided to help participants become employed. Since all participants in this study will be unemployed at the start of the study, this experience could help prepare participants for employment.

All participants will receive monetary incentives for attending the Therapeutic Workplace during the first 3 months of the study. Participants in the IPS Plus Abstinence-Contingent Wage Supplements group will get abstinence-contingent incentives for engaging in IPS supported employment and for obtaining and maintaining competitive employment. These incentives should increase attendance in the Therapeutic Workplace, development of job skills, employment, abstinence from heroin and cocaine, reduction in drug-related HIV risk behaviors. The earnings and payments could also have the benefit of providing a means of purchasing things that the family would not otherwise be able to afford.

The GMA component of the study is not expected to impart any direct benefit to participants.

Benefits to others. The study will evaluate the effectiveness, cost-effectiveness, and cost-benefit of IPS Plus Abstinence-Contingent Wage Supplements in increasing employment and promoting long-term cocaine abstinence. This novel intervention could be an effective and economically sound means of promoting long-term cocaine abstinence and employment in injection drug users, a population at considerable risk for a range of adverse outcomes including HIV because of their poverty, unemployment and continued injection drug use. If participants complete the job training and use IPS supported employment services, they could become employed which could reduce their need for government services. If employed, they could also contribute to the overall tax revenue generated in their community. If the job skills training and employment program increases the employment of participants, it could reduce their poverty and reduce transmission of poverty to their children. If the intervention is effective in promoting abstinence from cocaine and opiates, it could reduce injection drug use and drug-related HIV risk behaviors. This could reduce the risk of transmitting HIV infection in the community.

The GMA component of the study will address important questions raised by previous findings at the NIDA IRP (Epstein and Preston, 2012). The implication of those findings was that work might cause reductions in stress and drug craving during treatment for addiction. But before drawing treatment recommendations or policy recommendations from that finding, we need corroborative information collected under more controlled conditions. This Therapeutic Workplace study will provide that. The result should be more reliable recommendations.

Risk/Benefit Ratio. Overall, there are limited risks associated with this protocol above normal daily living. There are considerable potential benefits to the participants in this study, to people living with the participants, and to the community at large. Overall, the risk/benefit ratio appears highly favorable.

10. Payment and Remuneration

All incentives in this study will be provided by giving participants reloadable credits and adding incentives to the card when earned. Restrictions can be placed on these cards to restrict where they can be used to make purchases. We have been using these reloadable credit cards in our ongoing research and they have proved attractive to participants and convenient for staff to manage.

Phase 1 Training Incentives. All participants will be invited to attend the Therapeutic Workplace for 4 hrs every weekday for about 3 months (12 weeks), where they can earn about $10/hr for participating in our job skills or health education training program.

Some participants may get jobs in the community before their participation in the therapeutic workplace ends (i.e., before Phase 1 ends) and may have to stop attending our workplace to maintain their outside employment. Thus, we may offer wage supplements to participants who get jobs during Phase 1. Under the wage supplement procedure, participants would be able to earn a wage supplement for all hours that they work in a community job (up to our current maximum of 20 hours per week) as long as they continue to meet their drug abstinence requirements. The amount of the wage supplements will be equivalent to the current base pay hourly wage that participants can earn for working in the workplace. In total, participants will be able to earn $2,400 in Phase 1.for training in the workplace and/or for wage subsidies. The amounts will vary depending on each participant's productivity and the number of hours worked.

Phase 2 Abstinence-Contingent Wage Supplements. Participants in the Abstinence-Contingent Wage Supplement group will be able to earn wage supplements of up to $8 per hour for up to 40 hours per week for 52 weeks. In total, participants in the Abstinence-Contingent Wage Supplement group will be able to earn up to $16,640 in wage supplements.

Participant payment for assessments. Assessments will be conducted for all participants at intake to determine eligibility and characterize the population, immediately prior to random assignment, periodically throughout the 3-month abstinence initiation period, every 30 days throughout the 12-month intervention evaluation period after random assignment, and then at 3, 6, 9 and 12 months after the end of the intervention evaluation period. Participants will be paid $30 for the intake and pre-random assignment assessments, $30 for each monthly assessment during the 3-month abstinence initiation period and the 12-month intervention evaluation period, and $50 for the each assessment conducted 3, 6, 9 and 12 months after the end of the intervention evaluation period. In total, participants will be able to earn up to $710 for completing the assessments in this study.

Participant referral fees. As in our previous studies, participants will have the optional opportunity to earn incentives for referring people who are interested in the study. If a referral attends the initial

screening appointment and completes the necessary assessments, the participant who referred the person will receive up to $20. If a referred person enrolls in the main study, the participant who referred the person will receive up to $40 for making the referral.

GMA-related payments. Participants can earn:

- $ 5 / day ($2.50 for each drug/urine day) if urine is negative for cocaine and heroin/opioids and no self-reported use for either drug on smartphone OR if urine is positive for either cocaine or heroin/opioids and there is self-reported use (on smartphone) of the drug for which the participant tested positive (i.e., if urine positive for cocaine, must have self-reported cocaine use, etc.). Payment is only made for corresponding urines and smartphone self-reports; no payment is made for non-corresponding data. When a urine sample is missed or no data is able to be retrieved from the smartphone and there is no evidence for a malfunctioning smartphone is found, there will be no payment for that day.
- $30 / week will given if at least 82% of random prompts are answered during that week (regardless of drug-use entries)
- $5 / week will given if the participant presents the charged phone at all study visits during the week
- While credit is accumulated for each urine/smartphone correspondence, which occurs 3x weekly, participants may only be paid 1 time per week.
- The participant will receive $200 for return of the smartphone.

Participants can earn up to $50/week for about 12 weeks for compliance with GMA entries and carrying and charging the smartphone, and $200 for returning the smartphone for a total maximum remuneration of $800. Airtime on the smartphone for the 12-week period has a value of approximately $120. Payment will be made in cash.

Quality of life monitoring payments. Participants can earn up to $10 per week for answering questions in the Delight Me application. Each week, participants can earn $5 if they answer the majority of daily-administered questions and $5 if they answer a majority of the weekly-administered questions. Payment will be made in cash.

11. Costs

There will be no costs to participants for any services or treatment provided in this study. All procedures in the study will be paid for out of grant funds.