This supplement contains the following items:
1. Original protocol, final protocol, summary of changes.
2. Original statistical analysis plan, final statistical analysis plan, summary of changes

Note: This study (NCT02360007) was originally registered on 9/8/14 with the first participant enrolled on 11/13/14. However, on 11/12/14 the university hospital (the organization under whom this trial was registered) underwent a formal name change from Fletcher Allen Health Care to University of Vermont Medical Center, thus requiring a new clinical registry account to be established in early 2015.

CHRMS 14-063 Original Protocol:

Interim Treatment: Leveraging buprenorphine + technology to bridge waitlist delays

Principal Investigator: Stacey Sigmon, Ph.D.

STUDY PROTOCOL

Interim Treatment: Leveraging buprenorphine + technology to bridge waitlist delays

Principal Investigator: Stacey Sigmon, Ph.D.

INTRODUCTION

Opioid abuse is a significant national and international public health problem (European Monitoring Centre for Drugs and Drug Addiction, 2010; SAMHSA, 2010a). Opioid-related consequences include emergency department visits, drug overdoses, premature death, criminal activity, lost workdays and economic costs that in the U.S. exceed $56 billion annually (Becker et al., 2008; Birnbaum et al., 2011; Clausen et al., 2009; Hser et al. 2001; Shah et al., 2008; Wisniewski et al., 2008). Agonist maintenance is the most efficacious treatment for opioid dependence and dramatically reduces morbidity, mortality and spread of infectious disease (Ball & Ross, 1991; Johnson et al., 2000; Stotts et al., 2009). However, demand for treatment far exceeds available capacity (Friedmann et al., 2003; Wenger & Rosenbaum, 1994). Due to inadequate public funding, unfavorable zoning regulations and requirements for comprehensive care in programs that increase their cost, an alarming number of methadone clinics nationally and internationally have extensive waitlists (Des Jarlais et al., 1995; Fountain et al., 2000; Gryczynski et al., 2009; Peles et al., 2012, 2013; Peterson et al., 2010). Barriers to treatment access are not limited to methadone clinics. While approval of office-based BUP treatment extended agonist maintenance into general medical practices, many areas of the country have an insufficient number of willing providers, in part due to physicians' concerns about induction logistics, reimbursement challenges, potential for medication diversion, lack of support for providers and lack of psychosocial services for patients (Barry et al., 2008; Becker & Fiellin, 2006; Kissin et al., 2006; Netherland et al., 2009). The result is that opioid-dependent patients can remain on waitlists for years and are at significant risk for illicit drug use, criminal activity, infectious disease, overdose and mortality during this delay to treatment (Adamson & Sellman, 1998; Clausen et al., 2009; Cooper, 1989; Darke & Hall, 2003; Schwartz et al., 2009; Warner-Smith et al., 2001; Wenger & Rosenbaum, 1994). Prolonged waits are also associated with reduced likelihood of treatment entry (Donovan et al., 2001; Festinger et al., 1995; Hser et al., 1998; Kaplan & Johri, 2000).

This represents a serious barrier to the widespread delivery of effective treatment for opioid dependence. While many geographic areas have experienced a persistent shortage in opioid-substitution treatment availability, particularly for patients who must wait for admission to a subsidized program (Schwartz et al., 2009, 2011), this problem is especially urgent in rural areas struggling with high rates of prescription opioid (PO) abuse and relatively few treatment options (Fortney & Booth, 2001; Lenardson & Gale, 2007; Rosenblum et al., 2011; Rounsaville & Kosten, 2000). In Vermont, for example, rates of PO abuse are among the highest in the country (TEDS, 2004; ONDCP, 2008; Schneider et al., 2009), yet our state's primary methadone service (for which Dr. Sigmon is Director) has a waiting list of 823 people and 1.5 years. Further, while Vermont is among the leaders in the country in per capita number of BUP providers (SAMHSA, 2006ab), the vast majority are willing to treat only a handful of patients and thus it is extremely difficult for individuals to find an available provider (Department of Vermont Health Access, 2012). A similar scenario is seen in other rural states. In Kentucky, for example, the public methadone clinic in Lexington has an average 2-year wait for treatment slots (M. Lofwall, University of Kentucky, personal communication).

One important effort to increase access to opioid treatment has been to offer interim methadone treatment (IMT) to those awaiting enrollment into a methadone program. In this paradigm, approved methadone clinics can provide medication without accompanying psychosocial services on a temporary basis when only a waiting list would be otherwise available (IOM, 1995). IMT reduces drug use and drug-related risk behaviors during the prolonged wait for treatment access (Gruber et al., 2008; Schwartz et al., 2006, 2007, 2008, 2009a,b, 2011; Yancovitz et al., 1991). In the first experimental investigation, for example, 319 heroin-dependent participants were randomly assigned to IMT (n=199) or a waiting list control (n=120; Schwartz et al., 2006). Compared to waitlist controls, IMT participants provided significantly fewer heroin-positive urines, reported greater reductions in illegal activity and were more likely to eventually enter methadone treatment. In brief, providing IMT as opposed to a waitlist when a formal treatment slot is not readily available reduces drug-related risks and costs to the patient and for society more generally.

Despite these promising outcomes, methadone's regulatory and pharmacological features constrain the ability of IMT to significantly expand access to much-needed treatment. Methadone treatment in the U.S. is limited to licensed specialty clinics, it requires frequent clinic visits, and the medication itself has risks of

diversion, abuse and overdose (Luty et al., 2005). IMT regulations mandate that patients ingest all doses under direct observation, thus requiring daily clinic visits (IOM, 1995). They also limit the duration of IMT to no more than 120 days, with clinics required to discharge patients at that time or admit them to standard methadone treatment if a slot has become available. These constraints are incompatible with an environment of already-constrained resources and severely limit the ability of IMT to increase treatment access.

Our overarching goal is to develop a novel Interim Buprenorphine Treatment (IBT) that can bridge delays in access to life-saving treatment. Our integrative treatment package includes three key components, each strategically chosen to maximize patient access to efficacious medication while minimizing risk of nonadherence, abuse and diversion:

(1) Buprenorphine. The partial opioid agonist buprenorphine (BUP) was approved by the FDA in 2002 for the treatment of opioid dependence and exhibits a pharmacological profile that offers several advantages over other medications for treating opioid dependence (Bickel & Amass, 1995; Johnson et al., 2003). A ceiling on its agonist activity may reduce abuse liability and contribute to a superior safety profile (Banks, 1979; Jasinski et al., 1978; Lewis, 1985; Mello & Mendelson, 1980; Walsh et al., 1994, 1995). BUP also attenuates the effects of other opioids, thus suppressing illicit use during treatment (Bickel et al., 1988; Jasinski et al., 1978; Mello & Mendelson, 1980; Mello et al., 1982; Rosen et al., 1994; Walsh et al., 1995). Finally, BUP is available without the rigid dosing regulations and 120-day interim-dosing limit required for methadone. Taken together, BUP is uniquely compatible with an interim-dosing approach to treating opioid dependence.

Despite this impressive set of therapeutic features, only a single study has evaluated BUP's utility in an interim treatment paradigm. That trial was conducted in Oslo, Norway over a decade ago with 106 heroin-dependent individuals awaiting methadone treatment (Krook et al., 2002). Participants were randomized to receive BUP (n=55) or placebo (n=51) for 12 weeks, without psychosocial support. BUP was associated with significantly greater retention (Figure 1), with BUP and placebo participants retained for 42 vs. 14 days, respectively. Self-reported heroin use, assessed via a visual analogue scale ranging from 0 (Drug Free) to 10 (Daily Heavy Drug Abuse), was also significantly lower in the BUP vs. placebo group (Figure 2).

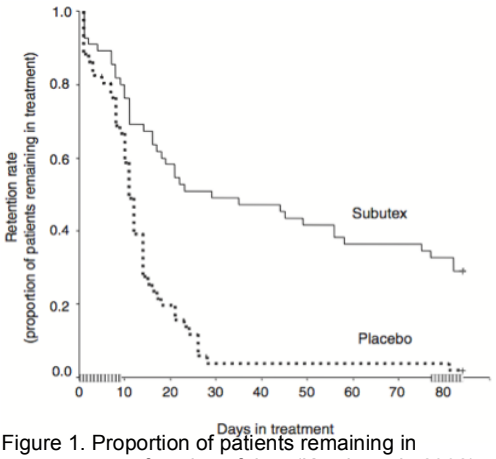

Figure 1. Proportion of patients remaining in treatment as a function of time (Krook et al., 2002)

Though this study provided encouraging initial support for BUP's role in interim treatment, it suffered from several important methodological limitations. While the BUP group demonstrated superior retention, attrition was still high with two-thirds of patients having dropped out by Week 12. The authors also used no objective measure of opioid abstinence, relying instead on patients to rate their recent opioid use via visual analogue scales. Finally, the study required near-daily clinic visits (Monday-Saturday) for observed dosing, which still translates to a resource-intensive treatment that fails to capitalize on BUP's favorable pharmacological profile.

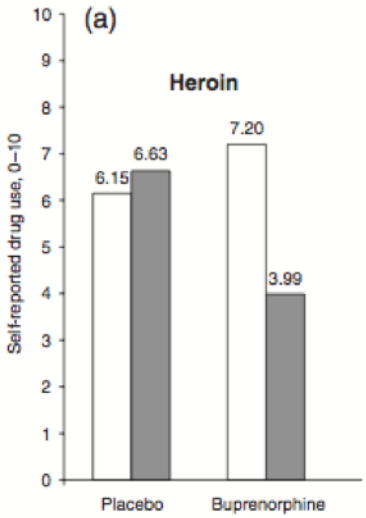

Figure 2. Self-reported severity of heroin use via VAS at baseline (open bars) and during entire 12-week study (filled bars)(Krook et al., 2002)

We propose that a thoughtfully developed treatment package that integrates BUP with innovative technology-based components can produce an IBT that truly expands treatment access while minimizing nonadherence and eliminating the need for daily visits. Below we describe the additional components that we will strategically combine to create this novel IBT protocol.

(2) Computerized adherence monitoring. While BUP's pharmacological profile makes it an excellent fit with an interim dosing arrangement, concerns about possible nonadherence, abuse or diversion could limit its widespread use in clinical settings (Fiellin et al., 2006; Johanson et al., 2012; Sigmon et al., 2004). Thus, the proposed IBT intervention will use computerized adherence monitoring (CAM) to promote adherence and minimize risk of diversion. Electronic medication dispensers have been used for many years to monitor and improve adherence in clinical populations in whom compliance is often poor, particularly antiretroviral therapy adherence among HIV-positive patients with concurrent substance abuse or psychiatric illness (e.g., Arnsten et al., 2001; Badiee et al., 2012; Wall et al., 1995). These studies have

typically used computerized caps placed on prescription bottles (e.g., Medication Event Monitoring System (MEMS), Aprex Corporation, Fremont, CA). Patients are instructed to remove only one dose at a time and to use only the MEMS bottle to dispense their medication. The cap contains a microprocessor that records the date and time of each opening. Only one study has used MEMS caps in BUP treatment, though not as its primary focus (Fiellin et al., 2006). That trial sought to compare varying intensities of counseling and medication monitoring in patients receiving BUP maintenance in primary care. Patients attended the clinic once vs. thrice weekly, received their remaining doses in pill bottles with MEMS caps, and were considered adherent for a given day if there was a recording of the bottle having been opened. BUP adherence was moderate (71% of study days), varied widely across patients, and was significantly correlated with illicit opioid abstinence. The authors concluded that this variability highlights the need to measure BUP adherence in future research and to monitor and encourage adherence in clinical practice to improve treatment outcomes.

While MEMS caps offer important benefits, they also have substantive limitations. The pill bottle given to patients contains all of the doses for the given period (e.g., week or month) and thus patients have access to the entire prescription each time they open it. Additionally, the cap only records a time-date stamp for each opening rather than the number of pills removed. A patient could, therefore, remove more than the prescribed amount at one time, replacing it with illicitly-obtained medication at a subsequent opening if s/he is called in for a pill count. This issue is especially important when dealing with pharmacotherapies for opioid dependence. That is, while the primary concern with HIV-positive patients is that they will simply fail to take their medication, with opioids there is the additional serious concern regarding potential for abuse (e.g., taking more than prescribed) or diversion (e.g., sharing or selling doses) of medication.

An important and exciting advance is the recent development of portable, disk-shaped devices that hold multiple-day doses across separate secure cells. The Med-O-Wheel Secure device, for example, accommodates doses for up to 28 days, with each day's dose secured in its own locked compartment around the dosage cassette (Addoz, Forssa, Finland; Figure 3). Each day's dose is available for a 3-hour window around a predetermined dosing time, during which the patient can press a button to prompt the appropriate compartment to move into an accessible position. Once this time window has ended, the device transitions into a "closed" mode automatically and tablets become inaccessible until the next preset time. It also includes locks and alarms to prevent tampering and access to tablets outside the preset time window. The Med-O-Wheel has begun to be used clinically in Finland in the hopes of reducing the general availability of illegal BUP, with recent reports noting favorable feasibility and acceptance by patients and staff (Tacke et al., 2009; Uosukainen et al., 2013). However, to our knowledge, the proposed study would be the first to directly evaluate this device as a component of BUP treatment for opioid dependence.

Figure 3.

(3) <u>Urinalysis and adherence monitoring</u>. Biochemical verification, typically via urine toxicology, is the most accurate and objective method for evaluating recent drug use (Chermack et al., 2000; Fendrich et al., 2004; Kilpatrick et al., 2000; Preston et al., 1997; Wish et al., 1997). Our long-standing protocol with illicit drug abusers involves thrice-weekly urinalysis (UA) monitoring during the early months of treatment (e.g., Sigmon et al., 2013; Higgins, Sigmon et al., 2003), often followed by a reduction to twice weekly once patients are stable in treatment. The patient provides a specimen under staff observation which first undergoes validity testing (e.g., appropriate temperature and concentration, no adulterants present). It is analyzed on-site via enzyme multiplied immunoassay (Microgenics, Fremont, CA) for the primary drug (e.g., opioids). One randomly-selected sample each week is also analyzed for other illicit drugs (e.g., cocaine, amphetamines, benzodiazepines, marijuana, barbiturates). Taken together, these features produce a rigorous UA monitoring protocol with a high likelihood of detecting even low levels of drug use.

While higher-frequency monitoring maximizes detection of drug use (Cone & Dickerson, 1992), thrice-weekly visits are incompatible with IBT specifically and with resource-constrained settings more generally. To balance the rigor of the above UA procedure with the less-intensive schedule necessary for IBT, we will develop a UA protocol that utilizes a random sampling approach. In this arrangement, patients are contacted at random times and instructed to visit the clinic for urine testing (Manno, 1986). Random sampling increases the effectiveness of UA monitoring, as patients are always in the position of not knowing when the next screen will be requested, reducing the possibility that s/he can tailor drug use to subvert monitoring (e.g., discontinue use long enough prior to a scheduled visit to test negative; Harford & Kleber, 1978).

We will develop a novel call-back program that will contact participants on a schedule generated

using a computerized random number algorithm. The participant will be instructed to return to the clinic within 12 hrs to provide a staff-observed urine specimen. They will also present their CAM device for inspection by staff to further ensure there is no evidence of tampering, nonadherence or diversion. This protocolized component will provide a rigorous yet efficient approach for supporting abstinence and adherence over an extended period of lower-frequency clinic visits.

Summary

Despite the undisputed effectiveness of agonist maintenance for opioid dependence, current capacity is inadequate to meet demand in the U.S. and internationally. There is a critical need to develop new and creative approaches for bridging gaps in treatment access. In this pilot study, we propose to develop an integrative interim BUP treatment that will increase access to pharmacotherapy for opioid dependence while reducing risk of nonadherence, abuse and diversion by leveraging state-of-the-art technology and rigorous, evidence-based methodology to verify protocol adherence. The overarching goal and specific aims of the project are directly relevant to our mission of improving the accessibility, implementation and effectiveness of drug abuse treatment.

INNOVATION

This project is highly innovative in at least four important ways: **(1)** By facilitating the eradication of waitlists for opioid treatment, this research represents a significant departure from the status quo and stands to produce a fundamental shift in how treatment of opioid dependence is conceptualized and delivered. **(2)** Our use of BUP is also a novel feature of the proposed study, as it will be the first to rigorously integrate a medication with fewer regulatory and pharmacological constraints into an integrative interim treatment model to mitigate delays in treatment access. **(3)** We propose to develop one completely novel treatment components (i.e., random call-back algorithm for UA and adherence monitoring) for this project. We also will refine three additional components (i.e., interim BUP dosing, CAM) in ways that will significantly enhance their disseminability. The development and/or refinement of each of these features individually will represent an important and innovative methodological advance in this area of research. Further, the unique combination of these components will produce an integrative treatment package for opioid dependence that is entirely novel. **(4)** The proposed research will extend our scientific knowledge about interim agonist treatment to new populations and new settings. First, all prior studies on interim opioid treatment have been with heroin-dependent patients (Krook et al., 2002; Schwartz et al., 2006, 2007, 2009, 2011). While we will not explicitly exclude heroin users, we know from our waitlist data that the majority of participants will be primary PO abusers (70% vs. 30% endorse a PO vs. heroin, respectively, as their primary drug). Thus, this study will be the first to evaluate the feasibility and efficacy of interim dosing in primary PO abusers. Second, the prior interim treatment studies were conducted in predominantly urban areas (i.e., Baltimore; Oslo, Norway). This study will be the first to investigate the utility of IBT in the rural and suburban areas that stand to significantly benefit from it.

APPROACH

Preliminary Studies

Successful completion of this project will require access to opioid-dependent individuals, expertise in conducting opioid research and experience with the IBT components proposed. Below we describe how our team has the requisite expertise necessary to expeditiously conduct the research as proposed.

Access to opioid-dependent patients. We have ready access to the patients who stand to benefit most from IBT- that is, opioid-dependent individuals who experience significant economic and geographic barriers to treatment access. Dr. Sigmon is the Director of the first and largest opioid treatment program in Vermont, which is contiguous with our research clinics. The Chittenden Center (CC) opened in 2002, providing methadone to 50 patients. Under Dr. Sigmon's leadership, it has steadily grown over the past decade to now treat 470 patients and offer BUP in addition to methadone. Unfortunately, we also have 667 people currently on the clinic's waitlist. Of note, 68% of waitlisted individuals have Medicaid and 10% have no insurance, making this clinic's state-subsidized treatment slots their most likely (and often only) option for treatment. Also worth noting is that barriers to treatment access are not limited to those on waitlists. In a survey of *enrolled* CC patients, patients reported that their travel distance and time to and from the clinic was approximately 21.4 miles and 60 minutes, respectively, with 85% of patients having to visit the clinic daily and 40% relying on public transportation (Sigmon et al., in prep). Patients reported spending $48.84 per week on transportation-related costs to attend the clinic. A substantial number also reported missing $\geq$1 clinic visit and dose due to transportation- (23%), weather- (17%) or cost-related (8%) reasons. Finally, 22% of patients reported that travel time had interfered with their ability to maintain employment. These data highlight the potential for using IBT components to also support treatment engagement among already-enrolled patients. In summary, we have

access to and familiarity with the patients likely to benefit substantially from IBT, further supporting the generality of the proposed research to the larger population of opioid abusers awaiting treatment.

Expertise in opioid research. Our team has extensive experience conducting opioid research. One recent example is Dr. Sigmon's NIDA-funded R01 randomized controlled trial (RCT) examining the relative efficacy of BUP taper durations in prescription opioid (PO) abusers, which was recently published in *JAMA Psychiatry* (Sigmon et al., 2013). While agonist maintenance is the recommended treatment for most opioid-dependent patients, detoxification represents an important treatment option particularly in areas where access to maintenance is limited. We aimed to develop an outpatient detoxification protocol that surmounts the problems with attrition and relapse that typically plague such treatments. Following brief BUP stabilization, 70 PO-dependent adults were randomized to receive a 1-, 2- or 4-week taper followed by naltrexone. All received individualized behavior therapy and thrice-weekly UA monitoring. Opioid abstinence, retention and naltrexone ingestion were significantly greater in the 4- vs. 2- and 1-week conditions, suggesting that a meaningful subset of PO abusers may respond positively to a 4-week BUP taper+naltrexone treatment. Dr. Sigmon has also evaluated the safety, pharmacokinetics and efficacy of novel, sustained-release BUP formulations. This includes the first-in-human evaluations of a depot BUP formulation, which suppressed withdrawal and attenuated hydromorphone challenge for 4-6 weeks following a single administration (Sigmon et al., 2004b, 2006; Sobel et al., 2004). She also was site PI on trials evaluating a BUP implant that produces steady-state blood levels for 6 months (Beebe et al., 2012; Rosenthall et al., in prep).

We are also experienced in conducting research in the context of opioid-replacement clinics more generally. Dr. Sigmon has a NIDA R01 to develop an efficacious smoking cessation treatment for methadone- and BUP-maintained smokers and has completed a series of RCTs demonstrating its efficacy (Dunn et al., 2008, 2010; Sigmon & Patrick, 2012; Sigmon et al., in prep). She has conducted studies targeting cocaine use, counseling attendance and other clinical issues among methadone patients (Correia et al., 2005; Dunn et al., 2008, 2009; Rosado et al., 2005; Sigmon et al., 2004a; Sigmon & Stitzer, 2005; Stitzer & Sigmon, 2006). We have published numerous papers on the topic of opioid dependence more broadly, including efforts to better characterize PO abusers, to compare urban vs. rural opioid abusers and to guide physicians in the clinical management of opioid withdrawal and detoxification (Dunn et al., 2011, in prep; Heil et al., 2008; Sigmon, 2006, 2008; Sigmon et al., 2012, in prep). Finally, Dr. Sigmon is committed to expanding much-needed access to opioid treatment nationally and served as a collaborator with Dr. Charles Schuster on the Postmarketing Surveillance Project for Suboxone. On the state level, Dr. Sigmon serves on advisory boards to improve opioid treatment throughout Vermont (e.g., Prescription Monitoring Program, Committee to Revise the Vermont BUP Treatment Guidelines, Committee to Develop a Hub & Spoke BUP Treatment System).

Overview of Proposed Pilot Study

In this randomized trial, opioid-dependent adults currently awaiting agonist maintenance will be randomly assigned to (1) **Interim Buprenorphine Treatment** (IBT) or (2) a **Waitlist Control** (WLC). IBT participants will complete BUP induction in Week 1 (or longer if required), during which they will attend the clinic daily. Thereafter, during Weeks 2-12 IBT participants will visit the clinic every two weeks to ingest their BUP dose, provide a urine specimen and receive their remaining doses in the Med-O-Wheel. WLC participants will remain on the waitlist for their treatment of choice. Participants in both conditions will complete follow-up assessments and provide a urine specimen at 4, 8, 12, 18 and 24 weeks after trial entry. WLC participants who have not entered treatment by Week 12 will be offered IBT at that time, providing an additional within-subject evaluation of IBT effects. Thus the overall possible study duration may vary between 12 - 28 weeks. For example, participation will be 12 weeks for those participants randomly assigned to the 12-week IBT condition who then complete the study without receiving a BUP taper as they have identified a maintenance treatment slot that is available. It would be 16 weeks for IBT participants who then elect to receive a 4-week BUP taper at the end of the study. It would be 24 weeks for WLC participants who opt, at the end of their initial 12-week waitlist condition, to receive 12 weeks of IBT but then enter a treatment program immediately following the end of IBT. Finally, participation duration could be 28 weeks for WLC participants who subsequently receive IBT and then elect to receive 4-week BUP taper following the completion of IBT.

Treatment conditions will be compared on the primary outcomes of illicit opioid abstinence and psychosocial functioning (i.e., ASI subscale scores) at each during-treatment assessment. We hypothesize that IBT participants will demonstrate reduced illicit opioid use and criminal behavior compared to WLC participants. Among WLC participants who cross over to IBT at Week 12, we hypothesize that illicit opioid use and frequency of criminal behavior will be lower during their IBT vs. waitlist phase. Secondary IBT-specific outcomes will include feasibility, acceptability, BUP adherence, retention, other drug use and patient satisfaction.

Participants. The proposed study will be conducted in the UVM Buprenorphine Research Clinic, which has been the site of BUP research for 25 years. The clinic is contiguous with our other research clinics as well as our methadone clinic for which Dr. Sigmon is Director. Participants will be 70 opioid-dependent individuals who will be assigned randomly to IBT or WLC. The primary referral source will be an IRB-approved flyer given to all CC waitlist individuals. We can also circulate ads in the larger community to reach additional patients on wait lists for treatment. Additional sources will include the Vermont State Alcohol and Drug Abuse Office, physicians, local mental health centers, a toll-free number, public service announcements, advertisements in local and alternative newspapers and flyers placed throughout the community. We have used these sources in prior studies and anticipate no difficulties gaining access to the sample needed for this trial (Dunn et al., 2008, 2010; Sigmon et al., 2009, 2013, in prep).

For inclusion in the trial, participants must be ≥18 years old, in good health, meet DSM-IV criteria for opioid dependence, provide anopioid-positive urine and be currently waitlisted. To minimize disruption due to treatment becoming available during the study, we will limit enrollment to those who joined a waitlist in the prior 12 months. As 349 of the CC waitlist had been added in the past 12 months (29 per month), we do not expect this criterion to impede recruitment. Those with a significant psychiatric or medical illness that may interfere with consent or participation will be excluded, as will those who are pregnant or nursing. Females will be tested for pregnancy and, should a participant become pregnant during the trial, her participation will be terminated and she will be assisted with accessing treatment at the high-risk pregnancy clinic. Those dependent on sedative-hypnotics will be excluded, due to the medical risks and notably low success rates with sedative-dependent opioid abusers (Stitzer & Chutuape, 1999). Participants must provide written informed consent to participate. Those meeting the above criteria and interested in IBT will be eligible to participate.

Eligible participants will be randomly assigned to one of two 12-week treatment conditions: (1) Interim Buprenorphine Treatment (IBT; n=35) or (2) a Waitlist Control (WLC; n=35). Minimum likelihood allocation (Aickin, 1982) will be used to achieve balance between treatment groups on the characteristics likely to influence treatment outcomes. Stratification variables will include duration of time on waiting list, amount of opioids used per day, any past-month cocaine use, current alcohol dependence and current chronic pain. Current chronic pain will be operationalized as: (1) endorsement of the first question of the BPI (i.e., whether you have pain other than everyday kinds of pain) and (2) duration of pain ≥ 3 months (Sigmon et al., 2013; Weiss et al., 2010). This procedure has been used effectively in our prior trials with opioid- and cocaine-dependent patients (Bickel et al., 1997; Higgins et al., 1994b; Sigmon et al., 2009, 2013).

Assessments. Participants will complete an intake assessment that includes: a drug history questionnaire developed by our clinic; the Addiction Severity Index (ASI; McLellan et al., 1985); the psychoactive substance abuse disorder sections of the DSM-IV (Feingold & Rounsaville, 1995); the Brief Symptom Inventory (Derogatis, 1993); Brief Pain Inventory (BPI; Cleeland, 1989, 1990; Keller et al., 2004); Beck Depression Inventory (Beck et al, 1961); Beck Anxiety Inventory (Beck et al, 1988); Michigan Alcoholism Screening Test (Selzer, 1971); Fagerstrom Test of Nicotine Dependence (Heatherton et al., 1991); a computerized Delay Discounting task (Bickel & Marsch, 2001; Yoon & Higgins, 2008). We have used these instruments in prior studies (e.g., Dunn et al., 2008, 2010; Higgins, Sigmon et al., 2003; Sigmon et al., 2009, 2013, in prep).

At each visit, self-report of opioid and other drug use will be collected via Time-Line Followback (Sobell et al., 1988) and withdrawal and agonist effects assessed using the Clinical Institute Narcotic Assessment (Peachey & Lei, 1988). A modified version of the intake will be completed with all subjects at Weeks 4, 8, 12, 18 and 24 post-randomization. These follow-ups will also include a Patient Satisfaction Questionnaire (Fiellin et al., 2001, 2006) and a brief assessment of overall interest, clarity and perceived effectiveness of IBT (and its individual components) on a Likert-type scale from 1 to 7. We will also collect qualitative data on (a) what aspects of the therapy patients liked and which ones they disliked, (b) patient suggestions to make the interventions better, (c) the extent to which participants utilized the IBT components. Participants will receive $30 per assessment independent of urine results, which has permitted high levels of compliance in our prior studies with illicit drug abusers (Higgins, Sigmon et al., 2003; Sigmon et al., 2009, 2013).

Interim Buprenorphine Treatment (IBT, n=35). Participants assigned to the IBT condition will complete an initial BUP stabilization week followed by IBT for 11 additional weeks. Participants will visit the clinic daily during Week 1 for induction onto an appropriate BUP dose. Thereafter, they will visit the clinic once every two weeks to ingest their BUP dose, provide a urine specimen and receive their remaining doses in the Med-O-Wheel. Additional details about the treatment components are provided below:

(1) Buprenorphine. IBT participants will receive buprenorphine sublingual tablets (Amneal Pharmaceuticals). Medication will be ordered and managed through our hospital's investigational pharmacy, which has prepared medications for our prior NIDA grants (e.g., Sigmon et al., 2009, 2013). BUP induction will

occur in Week 1 (or longer if required), during which participants will attend the clinic daily. Self-report and observer ratings of withdrawal and agonist effects will be completed at each visit, and urine and breath samples will be collected to ensure no recent use of drugs contraindicated with BUP. Individualized induction will be conducted using a protocolized approach (Johnson et al., 2003; Sigmon et al., 2009, 2013). During Weeks 2-12, participants will visit the clinic once every two weeks to ingest their dose, provide a urine specimen and receive their remaining 13 doses dispensed in the Med-O-Wheel for ingestion at home. They can also return to the clinic between scheduled visits if any concerns arise or if a dose evaluation is needed. At the end of the study, participants will be offered the 4-week BUP taper that was shown in our prior RCT to produce favorable outcomes (Sigmon et al., 2013) or, if a treatment slot has become available at their desired clinic, we will work with clinic staff to ensure a smooth transition to that program. If the participant elects to receive the 4-week buprenorphine taper, we will use the same procedures used in the aforementioned study (CHRMS 06-213/Sigmon et al., 2013), which will include daily visits, daily dosing of gradually-decreasing BUP doses and provision of non-opioid ancillary medications (e.g., clonidine, hydroxyzine) as needed for managing any opioid withdrawal symptoms.

(2) Computerized adherence monitoring. At each visit during Weeks 2-12, participants will receive their next 13 doses in the Med-O-Wheel device (Addoz, Forssa, Finland). Each day's dose will be secured in separate individually-locked compartments and the device will permit access during a 3-hour time window each day. Participants will be instructed to bring the device with them to each study visit, as well as random call-backs (below). They will be advised at intake and during Week 1 that any evidence of inappropriate CAM device use or suspicion of tampering with doses will be grounds for discharge from the study. Any participant failing to present the device on the first offense will be given a one-time opportunity to return within 12 hours with the intact Med-O-Wheel. Failure to do so, or a second offense, will result in termination of participation.

(3) Urinalysis and adherence monitoring. Random call-backs will occur approximately twice per month (or more often if determined necessary by the PI), during which participants will be contacted and instructed to return to the clinic within 12 hours. At each call-back, participants will provide a staff-observed urine specimen which will be analyzed immediately via enzyme multiplied immunoassay (Microgenics, Fremont, CA) for opioids (e.g., methadone, BUP, oxycodone, hydrocodone, heroin) and other drugs (e.g., cocaine, amphetamines, benzodiazepines, marijuana, barbiturates). Breath alcohol samples will also be analyzed at the time of UA testing (ALCO-SENSOR III, Intoximeters, Inc., St. Louis, MO). Participants will also present their CAM device for inspection by staff to further ensure there is no evidence of tampering or nonadherence.

Waitlist control (WLC, n=35). Participants assigned to the WLC will remain on the waiting list for their treatment of choice. They will visit the clinic to complete follow-up assessments and provide staff-observed urines according to the same schedule as IBT participants (Weeks 4, 8, 12, 18, 24). WLC participants who have not entered agonist treatment by Week 12 (which we anticipate to be the majority) will be offered the opportunity to receive IBT for an additional 12-week period as described above. This will permit an additional within-subject opportunity to qualitatively evaluate the size of IBT effects, as well as being an ethical strength by providing WLC participants the opportunity to receive active treatment.

Statistical Methods

Pilot testing findings will be summarized by descriptive statistics of illicit opioid abstinence, treatment component utilization, quantitative rating scales and qualitative summaries of comments and suggestions. For the RCT, IBT and WLC groups will be compared on baseline characteristics using analyses of variance for continuous and chi-square tests for categorical variables. If characteristics differ significantly and are predictive of outcome, they will be considered as potential covariates in subsequent analyses. Primary analyses will include all randomized subjects independent of early dropout, consistent with an intent-to-treat approach (Armitage, 1983). Repeated measures analyses for categorical data based on generalized estimating equations (SAS, PROC GENMOD) will be used to compare IBT and WLC on percentage of subjects abstinent for illicit opioids across Week 4, 8, and 12 assessments. Chi square tests will be used to compare abstinence at each time point. Analyses of variance (SAS, PROC MIXED) will be used to compare groups on continuous outcomes (e.g., illicit opioid use, ASI subscale scores). We hypothesize that IBT participants will demonstrate greater reductions in illicit opioid use and criminal behavior than WLC participants. Additional repeated measures analyses will be performed within the IBT group that include the Week 18 and 24 assessments to examine temporal patterns associated with abstinence during- and post-treatment. For WLC participants that cross over to IBT at Week 12, treatment condition will be represented by a within-subject factor in the generalized linear model. We hypothesize that illicit opioid use and criminal behavior will be significantly lower during their IBT vs. waitlist phase. Additional qualitative analyses will be used to characterize IBT-specific

outcomes, including feasibility, acceptability, BUP adherence and retention. Analyses will be performed using SAS statistical software, V9.3 (SAS Institute, Cary, NC).

Sample Size Justification

Statistical significance will be determined based on α=.05 for all analyses. The proposed sample of 70 subjects is based on having sufficient power for detecting a group difference on the percent of participants negative for illicit opioids at Week 12. Power is estimated to be 90% using α=.05 if the true abstinence rates are 60% vs. 20% for the IBT and WLC groups, respectively. These estimates are based on the IMT study by Schwartz et al. (2006), with slightly higher abstinence expected in our IBT condition as it is more intensive than the intervention used in that trial.

HUMAN SUBJECTS RESEARCH

Protection of Human Subjects

The proposed study will be conducted at a single site, the Substance Abuse Treatment Center at the University of Vermont. The study will take place after complete review and approval by the local Institutional Review Board (IRB), the UVM Office of the Committee for Human Research in the Medical Sciences (CHRMS).

1. Risks to the Subjects

a. Human Subjects Involvement and Characteristics. Participants will be males and females who are currently awaiting methadone or buprenorphine maintenance treatment for opioid dependence. Participants must be ≥18 years old, in good health, meet DSM-IV criteria for opioid dependence, provide an opioid-positive urine at intake, and be currently waitlisted. To minimize the chance that participation will be disrupted due to a treatment slot becoming available during the 12-week study, we will limit enrollment to those who joined the waitlist in the prior 12 months. As noted earlier, 349 of the current CC census had joined the waitlist in the past 12 months (approximately 29 per month); thus, we do not expect this criterion to impede recruitment of the proposed 70 participants for this study. Those with a significant psychiatric (e.g., psychosis, manic-depressive illness, organic psychiatric disorders) or medical (e.g., cardiovascular disease) illness that may interfere with consent or participation will be excluded, as will those who are pregnant or nursing. Females will be tested for pregnancy prior to and during the study. Should a participant become pregnant during the trial, her participation will be terminated and she will be assisted with accessing treatment at the medical center's high-risk pregnancy clinic. Those dependent on sedative-hypnotics will also be excluded, due to the medical risks and notably low success rates with sedative-dependent opioid abusers (Stitzer & Chutuape, 1999). Participants must provide written informed consent to participate. Those meeting the above criteria and interested in an IBT study will be eligible for participation. Subjects are not a "vulnerable population" as defined by human subject's protection guidelines; that is, they are not pregnant women, under legal coercion or restriction, or mentally impaired. They are competent adults who provide their voluntary informed consent.

Study procedures will be conducted at UVM Buprenorphine Research Clinic, which has been the site of BUP research for the past 25 years. The clinic is located in our University Medical Center's outpatient building and is contiguous with our other research clinics for cocaine dependence and smoking cessation as well as our methadone clinic for which Dr. Sigmon is Director. Participants in the randomized trial will be 70 opioid-dependent individuals. Study involvement will include participation in a 12-week randomized controlled trial in which 70 opioid-dependent adults wait-listed for agonist maintenance are randomized to receive IBT (n=35) or continue in a Waitlist Control condition (WLC; n=35). IBT participants will visit the clinic every 2 weeks while receiving the IBT package described above. WLC participants will remain on the waitlist for their treatment of choice, though they will complete the same scheduled follow-up assessments as IBT participants. WLC participants who have not entered treatment by Week 12 will be offered the opportunity to cross over to IBT at that time, contributing additional within-subject data with which to evaluate the efficacy of the IBT intervention.

b. Sources of Materials. Research materials will include questionnaires, structured clinical interviews, expired air samples for analyzing breath alcohol levels, urine samples for analyzing recent drug use and pregnancy status. All data will be collected for research purposes only. All data collection will be conducted by a trained bachelor's-level Research Assistant (RA) with special training on all forms and procedures. All information will be reviewed by the PI, who will determine participant eligibility and complete informed consent with eligible and willing participants. Subject data will be maintained in secure filing cabinets behind locked doors in order to protect confidential subject information. Safe places will include locked filing cabinets or locked rooms that will be accessible only to study personnel. Full subject names will not be listed on the outside of the binders in order to protect the identity of study participants. Subject data and subject identifiers will only be accessible to approved research staff.

c. Description of Potential Risks. Risks include breach of confidentiality and any side effects associated with the study medication (i.e., buprenorphine).

Breach of confidentiality. Study data include medical and psychiatric histories and biological measures of alcohol and illicit drug use and pregnancy. The likelihood of a breach of confidentiality is low as we will take precautions to minimize this risk as described below under Adequacy of Protection against Risk.

Side effects of buprenorphine. The side effects of buprenorphine include light-headedness, dizziness, sedation, lethargy, changes in sexual ability, nausea, vomiting, sweating, euphoria, constipation, respiratory depression, flushing of the face, skin itchiness or redness, darkening of the skin and/or swelling, bradycardia, headache, yawning, tearing, runny nose, muscle tremor, dilated or constricted pupil, restlessness, diarrhea, hypertension, hypotension, or potentially elevated liver enzyme levels (particularly among subjects with a history of hepatitis). The administration of the partial opioid agonist, buprenorphine, in individuals physically dependent on opioids should not result in acute toxicity because these individuals are tolerant to such drug effects. There also is a ceiling on the agonist effects of partial agonists; thus, the agonist effects of the partial agonist, buprenorphine, are considered to be safer than full agonists. Because buprenorphine is a partial agonist, it could also function as an antagonist and promote withdrawal symptomatology. We will administer buprenorphine in accordance with standard practice (see Methods) and, based on our previous experience in treating opioid-dependent individuals with this medication (Sigmon et al., 2009; Sigmon et al., 2013, *JAMA Psychiatry*), we do not anticipate that buprenorphine-precipitated withdrawal or sedation will pose a problem.

2. Adequacy of Protection Against Risks

a. Recruitment and Informed Consent. The primary referral source will be distribution of an IRB-approved flyer to all CC waitlist individuals informing them about the study. Should this recruitment method ever become insufficient, we can also circulate ads throughout the larger community in order to reach additional patients on wait lists for BUP maintenance via OBOT. Additional sources will include self-referrals, drug abuse clinics, the Vermont State Alcohol and Drug Abuse Office, physicians, local mental health centers, a toll-free number, public service announcements, advertisements in local and alternative newspapers and flyers placed throughout the community. We have successfully recruited participants using these sources in prior studies (Dunn et al., 2008, 2010; Sigmon et al., 2009, in prep, 2013) and anticipate no difficulties gaining ready access to the sample needed.

Contact between participants and study staff will be initiated by the participants. Potential participants will respond to mailings or advertisements that contain a study description and the name and phone number of the Research Assistant. When potential participants call the Research Assistant, s/he will briefly describe the study and use a brief phone screen to make a preliminary determination about the potential participant's eligibility. Those who are interested in participating and appear to be eligible will be schedule for a longer intake screening that will begin with a full study description of study procedures. Those interested in undergoing study screening will then be provided with a copy of the consent form to read as we go over it with them. Risks and benefits of the study will be described. Potential participants will be asked to paraphrase the consent form and will be asked questions to determine their understanding of key elements of the informed consent. Potential participants who wish to proceed with the interview will be asked to sign the interview consent form and will be given a signed copy of his/her signed consent form.

b. Protection Against Risk. (1) To protect confidentiality, the guidelines stated in Title 42 of the Code of Federal Regulations, Part 2, "Confidentiality of Alcohol and Drug Abuse Records" will be followed. As stated in these regulations, subjects will be given a notice of federal confidentiality requirements (which will be included in the consent form). All records will be locked in file cabinets kept on site behind locked doors. Except for intake material, subjects' names (i.e., first and last names) will not be attached to the data forms. A central code/data base linking subject number with subject names will be kept, which will be available only to specified staff.

(2) In order to protect participants from any adverse effects of buprenorphine, a number of safeguards will be in place. First and most generally, subjects will be screened thoroughly at intake using medical, psychiatric, drug abuse, and cognitive interviews and self-reports. They will have a complete physical exam, and follow-up interviews and tests may be ordered to clarify results. The results of all tests will be reviewed by the medical director (Dr. Brooklyn) and the PI (Dr. Sigmon). Thus, we will document that the patient is healthy to participate in the proposed study. To prevent subjects who may have an insufficient level of opioid dependence from participating in these studies, they will have to meet several criteria (e.g., DSM-IV criteria for opioid dependence and FDA qualification criteria for buprenorphine treatment, including a history of opioid dependence and significant current opioid use). All medication administration will occur during working hours at the University Health Center (UHC), an inpatient/outpatient facility of the University of Vermont College of Medicine and Fletcher Allen Health Care. Numerous physicians are on the same floor as the clinic. All nursing

and research staff will be trained by medical staff in detecting adverse effects. If a subject has any untoward effects, the Study Physician and PI will be contacted. Study Physician Dr. Brooklyn will be on-call continuously for advice and assistance in the event that adverse effects occur. Dr. Brooklyn has been working with our previous buprenorphine projects over the last 15 years, is a buprenorphine provider, is Medical Director of the Chittenden Clinic methadone program, and he has extensive experience with the clinical use of buprenorphine as a Vermont buprenorphine provider and trainer. The emergency room for the Fletcher Allen Hospital of Vermont is located approximately one block away from the UHC.

(3) Finally, patients are free not to participate in this study or to withdraw from it at any time. If they decide not to participate in the study, we will be glad to discuss with them other treatments that may be available in Vermont, including residential, outpatient, and medication-assisted treatment options. If patients choose to withdraw or are discharged from the study, they will have the option of receiving the 4-week buprenorphine detoxification that was demonstrated in our prior trial to be most effective (Sigmon et al., 2013, *JAMA Psychiatry*). If patients decide not to participate in this study or to withdraw from this study, their decision will not prejudice their future medical care at the University of Vermont or Fletcher Allen Health Care. The investigators also retain the right to terminate patients' participation in the study if in their judgment continued participation would put them in physical or psychological danger. Additional details on our data and safety monitoring of the proposed research to ensure the safety of subjects is provided in the below section entitled "Data and Safety Monitoring Plan".

3. Potential Benefits to Participants and Others

Volunteers may benefit by initiating abstinence from illicit opioids during their study participation, including experiencing a reduction in the wide range of medical, financial, psychosocial, and legal consequences associated with illicit opioid abuse. Volunteers may also benefit from the financial compensation provided as part of the proposed study. By improving treatment access for opioid abuse and dependence, the proposed research also stands to benefit public health in general by reducing the vast economic and societal costs associated with opioid abuse (e.g., health service utilization and costs, criminal activity, contraction of preventable diseases such as HIV and hepatitis). In addition, there are potential scientific benefits to be gained by expanding our empirical knowledge on how to mitigate gaps in treatment access among opioid-dependent individuals. Overall, the individual participant, the medical and scientific communities, and society in general may benefit by our efforts to develop an interim buprenorphine treatment for patients awaiting agonist maintenance. As such, the risks to which individuals may be exposed as a function of their research participation are reasonable in relation to the anticipated benefits.

4. Importance of the Knowledge to be Gained

The proposed project has the potential to contribute a novel and effective technology-assisted pharmacotherapy protocol that can be widely disseminated to bridge gaps in access to life-saving opioid treatment. Thus, knowledge gained from this research may significantly enhance the accessibility, implementation and effectiveness of drug abuse treatment more generally. Consequently, the risk/benefit ratio is favorable. The risks to which individuals are exposed as a consequence of their research participation are generally less than that associated with continuing their ongoing abuse of illicit opioids. In contrast, the potential and probable benefits to be derived by society in general and by opioid abusers as a group are considerable. In summary, conducting this research seems well justified.

DATA AND SAFETY MONITORING PLAN

The proposed study presents low risk to participants. Our overall monitoring plan consists of continuous, close monitoring by the PI and Co-Investigators, as well as prompt reporting of any adverse events (AEs) or serious adverse events (SAEs) to the UVM IRB/CHRMS and/or NIH, as suggested by Notice OD-00-038. We provide more detail below regarding particular areas recommended by PA-03-066 and Notice OD-00-038.

Patient eligibility and status. All intake data collection will be conducted by a trained bachelor's-level Research Assistant (RA) using specialized forms and procedures. Medical screening data will be reviewed by the Study Physician. All intake information will be reviewed by the PI, who will determine participant eligibility. Only trained and IRB-approved research staff will complete informed consent with eligible and willing participants. The status of all active participants will be reviewed at weekly meetings between the PI, Co-investigators and RAs.

Rigorous data management/Quality assurance. The majority of study data collection will be conducted using self-report questionnaires. Randomly selected data will be checked by the RAs for completeness and to ensure quality (i.e., no appearance of rote answers, etc.). In terms of standard operating procedures at the clinic, all assessments will be administered by trained research staff. All subject data will be maintained in secure filing cabinets behind locked doors in order to protect confidential subject information. Safe places will include locked filing cabinets or locked rooms that will be accessible only to study personnel. Full subject names will not be listed on the outside of the binders in order to protect the identity of study participants. Moreover, all data that are entered into spreadsheets and databases, in preparation for data analyses, will be entered twice. That is, two separate individuals will enter the data into databases, and a comparison between data entries will be conducted to detect data entry errors. All discrepancies in data entry will be checked against the raw data source, and the correct data entry will be used. All data that are entered into spreadsheets and databases will be coded by subject ID number and not by subject name. Additionally, all entered data will be backed up on an external hard drive or a secure project server at least weekly. The biostatistician and PI will discuss any problems at monthly data meetings. Additional meetings will be conducted on an as-needed basis. An original copy of the data will be retained at the clinic should anything happen to the document during transmission.

Auditing procedures. Review of any problems related to quality of data collection, transmission or analyses and of any AEs and SAEs that occurred during the past week will occur at weekly research staff meetings. Interim analyses of efficacy data will be conducted when half the subjects have been entered or at other times based on the joint discretion of the PI, Co-I and biostatistician.

Reporting mechanisms of AEs & SAEs to the CHRMS and NIDA. In the proposed study, we will use the FDA's definition of AEs and SAEs. AEs and SAEs will be assessed at each clinic visit by a trained RA and copies of all reports noting AEs and SAEs will be kept in a central file as well as in the individual subject's chart. AEs will be discussed at the weekly research staff meetings. Any SAE will be brought to the attention of the PI as soon as possible and not longer than 24 hrs. The NIDA project officer will be notified of SAEs within 72 hrs. Any SAE, whether or not related to study intervention, will be reported to the IRB's CHRMS using the University of Vermont Adverse Event Reporting Document within 5 days of the event. Copies of these reports will be forwarded to the NIDA Project Officer at the same time that they are sent to the CHRMS. This will be the responsibility of the PI. The CHRMS will make a determination as to whether additional reporting requirements are needed. CHRMS actions will be reported to NIDA by the PI no less than annually and more frequently as recommended by the local CHRMS. Any SAEs will be summarized in the yearly NIDA Progress Report, including a review of frequency and severity. All SAEs will be followed through ongoing consultation with the physician caring for the patient until they resolve, result in death, or stabilize and are not expected to improve.

Data Sharing Plan. After all data have been collected and the results of the study have been published, de-identified data will be made available to other qualified investigators upon request. The request will be evaluated by the PI and Co-Investigators to ensure that it meets reasonable demands of scientific integrity.

LITERATURE CITED

Abbott, P.J., Moore, B.A., Delaney, H.D., & Weller, S. (1999). Retrospective analyses of additional services for methadone maintenance patients. *J Subst Abuse Treat, 17*,129-137.

Abbott, P.J., Weller, S.B., Delaney, H.D., & Moore, B.A. (1998). Community reinforcement approach and relapse prevention in the treatment of opioid dependency. *Am J Drug Alcohol Abuse, 24*, 17-30.

Adamson, S. J., & Sellman, D. (1998). The pattern of intravenous drug use and associated criminal activity in patients on a methadone treatment waiting list. *Drug Alcohol Rev, 17*, 59−166.

Amass, L., Bickel, W.K., Crean, J.P., Blake, J., & Higgins, S.T. (1998). Alternate-day buprenorphine dosing is preferred to daily dosing in opioid-dependent humans. *Psychopharmacol, 136*, 217-225.

Amass, L., Bickel, W.K., Higgins, S.T., & Badger, G.J. (1994a). Alternative-day dosing during buprenorphine treatment of opioid dependence. *Life Sciences, 54*, 1215-1228.

Amass, L., Bickel, W.K., Higgins, S.T., & Hughes, J.R. (1994b). A preliminary investigation of outcome following gradual or rapid buprenorphine detoxification. *J Addict Dis, 13*, 33-45.

Arnsten, J.H., Demas, P.A., Farzadegan, H., Grant, R.W., Gourevitch, M.N., et al. (2001). Antiretroviral therapy adherence and viral suppression in HIV-infected drug users: Comparison of self-report and electronic monitoring. *Clin Infect Dis, 33*(8), 1417-1423.

Badiee, J., Riggs, P.K., Rooney, A.S., Vaida, F., Grant, I., et al. (2012). Approaches to identifying appropriate medication adherence assessments for HIV infected individuals with comorbid bipolar disorder. *AIDS Patient Care STDS, 26*(7), 388-394.

Ball, J.C., & Ross, A. (1991). *The effectiveness of methadone maintenance treatment*. New York: Springer-Verlag.

Banks, C.D. (1979). Overdosage of buprenorphine: case report. *NZ Med. J. 89*, 255–256.

Barry, D.T., Irwin, K.S., Jones, E.S., Becker, W.C., Tetrault, J.M., et. al. (2008). Integrating buprenorphine treatment into office-based practice: A qualitative study. *J Gen Intern Med, 24*(2), 218-225.

Beck, A.T., Epstein, N., Brown, G., & Steer, R.A. (1988). An inventory for measuring clinical anxiety: Psychometric properties. *J Consult Clin Psych, 56*, 893-897.

Beck, A.T., Ward, C.H., Mendelson, M., Mock, J., & Erbaugh, J. (1961). An inventory for measuring depression. *Arch Gen Psychiat, 4*, 561-571.

Becker, W. C., & Fiellin, D. A. (2006). Provider satisfaction with office- based treatment of opioid dependence a systematic review. *Subst Abuse, 26*, 15−22.

Becker, W.C., Sullivan, L.E., Tetrault, J.M., Desai, R.A., & Fiellin, D.A. (2008). Non-medical use, abuse and dependence on prescription opioids among U.S. adults: Psychiatric, medical and substance use correlates. *Drug Alc Depend, 94*, 38-47.

Beebe, K.L., Chavoustie, S., Ling, W., Sigmon, S., Leiderman, D.B., & Bailey, G. (2012). Buprenorphine implants for the treatment of opioid dependence: Six- and 12-month outcomes. Presented at the 51st annual meeting of the American College of Neuropsychopharmacology.

Bickel, W.K., Marsch, L.A., Buchhalter, A.R., & Badger, G.J. (2008). Computerized behavior therapy for opioid-dependent outpatients: a randomized controlled trial. *Exp Clin Psychopharmacol, 16*(2):132-43.

Bickel, W.K., & Marsch, L.A. (2001). Toward a behavioral economic understanding of drug dependence: Delay discounting processes. *Addiction, 96*, 73-86.

Bickel, W.K., & Amass, L. (1995). Buprenorphine treatment of opioid dependence: A review. *Exp Clin Psychopharmacol, 3*, 477-489.

Bickel, W.K., Amass, L., Higgins, S.T., Badger, G.J., & Esch, R.A. (1997). Effects of adding behavioral treatment to opioid detoxification with buprenorphine. *J Consult Clin Psych, 65*, 803-810.

Bickel, W.K., Stitzer, M.L., Bigelow, G.E., Liebson, I.A., Jasinski, D.R., et al. (1998). Buprenorphine: dose-related blockade of opioid challenge effects in opioid dependent humans. *J Pharmacol Exp Ther, 247*, 47–53.

Birnbaum, H.G., White, A.G., Schiller, M., Waldman, T., Cleveland, J.M. et al. (2011). Societal costs of prescription opioid abuse, dependence and misuse in the United States. *Pain Med, 12*(4), 657-667.

Boyer, E.W., Smelson, D., Fletcher, R., Ziedonis, D., & Picard, R.W. (2010). Wireless technologies, ubiquitous computing and mobile health: application to drug abuse treatment and compliance with HIV therapies. *J Med Toxicol, 6*, 212-216.

Centers for Disease Control and Prevention (CDC). (2008). Disease burden from Viral hepatitis A, B, and C in the United States. Division of Viral Hepatitis, National Center for HIV/AIDS, Viral Hepatitis, STD and TB Prevention. Accessed on 04/23/2013 at: http://www.cdc.gov/hepatitis/Statistics/index.htm

Centers for Disease Control and Prevention (CDC). (2011). HIV Surveillance Report: Diagnoses of HIV infection and AIDS in the United States and Dependent Areas, Vol. 23. Accessed on 04/23/2013 at: http://www.cdc.gov/hiv/topics/surveillance/basic.htm

Chermack, S. T., Roll, J., Reilly, M., Davis, L., Kilaru, U., et al. (2000). Comparison of patient self-reports and urinalysis results obtained under naturalistic methadone treatment conditions. *Drug Alcohol Depend, 59*(1), 43-49.

Clausen, T., Waal, H., Thoresen, M., & Gossop, M. (2009). Mortality among opiate users: Opioid maintenance therapy, age and causes of death. *Addiction, 104*, 1356-1362.

Cleeland, CS. (1989). Measurement of Pain by Subjective Report. Iss Pain Meas. Vol. 12. New York: Raven Press, pp 391–403.

Cleeland, C.S. (1990). Assessment of Pain in Cancer: Measurement Issues. *Proceedings of the Second International Congress on Cancer Pain*. Vol. 16. New York: Raven Press, pp 47–56.

Cone, E.J. & Dickerson, S.L. (1992). Efficacy of urinalysis in monitoring heroin and cocaine abuse patterns: Implications in clinical trials for treatment of drug dependence. *NIDA Res Monogr, 128*, 46-58.

Cooper, J. R. (1989). Methadone treatment and acquired immunodeficiency syndrome. *JAMA, 262*,1664–1668.

Copenhaver, M.M., Johnson, B.T., Lee, I.C., Harman, J.J., Carey, M.P., & SHARP Research Team. (2006). Behavioral HIV risk reduction among people who inject drugs: Meta-analytic evidence of efficacy. *J Subst Abuse Treat, 31*(2), 163-171.

Correia, C.J., Sigmon, S.C., Silverman, K., Bigelow, G., & Stitzer, M.L. (2005). A comparison of voucher delivery schedules for the initiation of cocaine abstinence. *Exp Clin Psychopharmacol, 13*, 253-258.

Crawford, A.G., Sikirica, V., Goldfarb, N., Popiel, R.G., Patel, M., et al. (2005). Interactive voice response reminder effects on preventive service utilization. *Am J Med Qual, 20*(6), 329-336.

Darke, S., & Hall, W. (2003). Heroin overdose: Research and evidence-based intervention. *J Urban Health, 80*, 189–200.

Department of Vermont Health Access (2012). Vermont hub and spoke health homes: Program and payment overview. State of Vermont Department of Health, http://dvha.vermont.gov/administration/1hub-spoke-health-home-framework-payment-12-10-12.pdf

Derogatis, L.R. (1993). Brief Symptom inventory. Minneapolis, MN: National Computer Systems, Inc.

Des Jarlais, D.C., Paone, D., Friedman, S.R., Peyser, N., & Newman, R.G. (1995). Regulating controversial programs for unpopular programs for unpopular people: Methadone maintenance and syringe exchange programs. *Am J Public Health, 85*, 1577−1584.

Donovan, D.M., Rosengren, D.B., Downey, L., Cox, G.B., & Sloan, K.L. (2001). Attrition prevention with individuals awaiting publicly funded drug treatment. *Addiction 96* (8), 1149–60.

Dunn, K., Sigmon, S.C., Saulsgiver, K., Patrick, M., Heil, S.H., et al. (in preparation). Characterizing opioid withdrawal severity and timecourse during double-blind, outpatient buprenorphine detoxification.

Dunn, K.E., Saulsgiver, K.A., Patrick, M.E., Heil, S.H., Higgins, S.T., & Sigmon, S.C. (submitted). Characterizing and Improving HIV and Hepatitis Knowledge Among Primary Prescription Opioid Abusers. *Drug Alcohol Depend*.

Dunn, K.E., Sigmon, S.C., Heil, S., & Higgins, S.T. (June 2008a). *Semi-quantitative buprenorphine testing in an ongoing study with prescription opioid abusers.* Poster presentation at the 70th Annual Meeting of the College on Problems of Drug Dependence, San Juan, PR.

Dunn, K.E., Sigmon, S.C., McGee, M.R., Heil, S.H., & Higgins, S.T. (2008b). Evaluation of ongoing oxycodone abuse among methadone-maintained patients. *J Subst Abuse Treat, 35*, 451-456.

Dunn, K.E., Sigmon, S.C., Reimann, E., Heil, S.H., & Higgins, S.T. (2009). Effects of smoking cessation on illicit drug use among opioid maintenance patients. *J Drug Issues, 39*(2), 313-328.

Dunn, K.E., Sigmon, S.C., Reimann, E.F., Badger, G.J., Heil, S.H., et al. (2010). A contingency-management intervention to promote initial smoking cessation among opioid-maintained patients. *Exp Clin Psychopharmacol, 18* (1), 37-50.

Dunn, K.E., Sigmon, S.C., Strain, E., Heil, S.H., & Higgins, S.T. (2011a). The association between outpatient buprenorphine detoxification duration and clinical treatment outcomes: A review. *Drug Alcohol Depend, 119* (1-2), 1-9.

Dunn, K.E., Sigmon, S.C., Thomas, C.S., Heil, S.H., & Higgins, S.T. (2008c). Voucher-based contingent reinforcement of smoking abstinence among methadone-maintained patients: A pilot study. *J Appl Behav Anal, 41*, 527-538.

Edelman, E.J., Dinh, A., Moore, B.A., Schottenfeld, R.S., Fiellin, D.A., et al. (2012). HIV testing practices among buprenorphine-prescribing physicians. *J Addict Med, 6;*159-165.

European Monitoring Centre for Drugs and Drug Addiction. (2010). *Annual report 2010: the state of the drugs problem in Europe.* Luxembourg: Publications Office of the European Union http://www.emcdda.europa.eu/attachements.cfm/att_120104_EN_EMCDDA_AR2010_EN.pdf

Fazzino, T.L., Harder, V.S., Rose, G.L., & Helzer J.E. (in press). A daily process examination of the bidirectional relationship between craving and alcohol consumption as measured via Interactive Voice Response (IVR). Alcohol Clin Exp Res.

Feingold, A., & Rounsaville, B. (1995). Construct validity of the dependence syndrome as measured by DSM-IV for different psychoactive substances. *Addiction, 90*, 1661-1669.

Fendrich, M., Johnson, T. P., Wislar, J. S., Hubbell, A., & Spiehler, V. (2004). The utility of drug testing in epidemiological research: Results from a general population survey. *Addiction, 99*(2), 197-208.

Festinger, D.S., Lamb, R.J., Kountz, M.R., Kirby, K.C., & Marlowe, D. (1995). Pretreatment dropout as a function of treatment delay and client variables. *Addict Behav, 20*(1),111–5.

Fiellin, D.A., Moore, B.A., Sullivan, L.E., Becker, W.C., Pantalon, M.J., et al. (2008). Long-term treatment with buprenorphine/noloxone in primary care: Results at 2-5 year follow-up. *Am J Addict, 17*, 116-120.

Fiellin, D.A., O'Connor, P.G., Chawarski, M., Pakes, J.P., Pantalon, M.V. et al. (2001). Methadone maintenance in primary care: A randomized controlled trial. *JAMA, 286*(14), 1724-1731.

Fiellin, D.A., Pantalon, M.V., Chawarski, M.C., Moore, B.A., Sullivan, L.E., et al. (2006). Buprenorphine maintenance in primary care: A randomized controlled trial of counseling conditions and medication dispensing. *NEJM, 355*(4), 365-374.

Fortney, J. & Booth, B.M. (2001). Access to substance abuse services in rural areas. *Recent Dev Alcohol, 15*:177-197.

Fountain, J., Strang, J., Griffiths, P., Powis, B., & Gossop, M. (2000). Measuring met and unmet need of drug misusers: Integration of quantitative and qualitative data. *European Addiction Research, 6*, 97−103.

French, M.T., McCollister, K.E., Cacciola, J., Durell, J., & Stephens, R.L. (2002a). Benefit-cost analysis of addiction treatment in Arkansas: specialty and standard residential programs for pregnant and parenting women. *Substance Abuse, 23*, 31-51.

French, M.T., Salome, H.J., Sindelar, J.L., & McLellan, A.T. (2002b). Benefit-cost analysis of addiction treatment: methodological guidelines and empirical application using the DATCAP and ASI. *Health Serv Res, 37*, 433-455.

Friedmann, P.D., Lemon, S.C., Stein, M.D., & D'Aunno, T.A. (2003). Accessibility of addiction treatment: Results from a national survey of outpatient substance abuse treatment organizations. *Health Serv Res, 38*(3), 887-903.

Gallalee, S., Sigmon, S.C. & Cope, M. (in preparation). Access to treatment for opioid abuse: A geographic analysis of Vermont.

García-Fernández, G., Secades-Villa, R., García-Rodríguez, O., Alvarez-López, H., Fernández-Hermida, J.R., et al. (2011a). Long-term benefits of adding incentives to the community reinforcement approach for cocaine dependence. *Eur Addict Res, 17*(3), 139-45.

García-Fernández, G., Secades-Villa, R., García-Rodríguez, O., Sánchez-Hervás, E., et al. (2011b). Adding voucher-based incentives to community reinforcement approach improves outcomes during treatment for cocaine dependence*. Am J Addict, 20*(5), 456-61

García-Rodríguez, O., Secades-Villa, R., Higgins, S.T., Fernández-Hermida, J.R., & Carballo, J.L. (2008). Financing a voucher program for cocaine abusers through community donations in Spain. *J Appl Behav Anal, 41*(4), 623-8.

Garcia-Rodriguez, O., Secades-Villa, R., Higgins, S.T., Fernandez-Hermida, J.R., Carballo, J.L., et al. (2009). Effects of voucher-based intervention on abstinence and retention in an outpatient treatment for cocaine addiction: A randomized controlled trial. *Exp Clin Psychopharmacol, 17*(3), 131-8.

Greenwald, M.L., Johanson, C.-E., Moody, D.E. , Woods, J.H., Kilbourn, M.R., et al. (2003). Effects of buprenorphine maintenance dose on u-opioid receptor availability, plasma concentrations, and antagonist blockade in heroin-dependent volunteers. *Neuropsychopharmacology*, 28*,* 2000-2009.

Gruber, V. A., Delucchi, K. L., Kielstein, A., & Batki, S. L. (2008). A randomized trial of 6-month methadone maintenance with standard or minimal counseling versus 21-day methadone detoxification. *Drug Alcohol Depend, 94*, 199-206.

Gryczynski, J., Schwartz, R., O'Grady, K., & Jaffe, J. (2009). Treatment entry among individuals on a waiting list for methadone maintenance. *Am J Drug Alcohol Abuse, 35*(5), 290-294.

Harford, R.J., & Kleber, H.D. (1978). Comparative validity of random-interval and fixed-interval urinalysis schedules. *Arch Gen Psychiatry, 35*(3), 356-359.

Heatherton, T. F., Kozlowski, L. T., Frecker, R. C., & Fagerström, K. O. (1991). The Fagerström Test for Nicotine Dependence: a revision of the Fagerström Tolerance Questionnaire. *Br J Addict, 86*(9), 1119-27.

Heil, S.H., Gaalema, D.E., Johnston, A.M., Sigmon, S.C., Badger, G.J., et al. (2012). Infant pupillary response to methadone administration during treatment for neonatal abstinence syndrome: A feasibility study. *Drug Alcohol Depend, 126*(1-2), 268-271.

Heil, S.H., Sigmon, S.C., Jones, H.E., & Wagner, M. (2008). Comparison of characteristics of opioid-using pregnant women in rural and urban settings. *Am J Drug Alcohol Dep, 34*, 463-471.

Heil, S.H., Sigmon, S.C., Mongeon, J.A., & Higgins, S.T. (2005). Characterizing and improving HIV/AIDS knowledge among cocaine-dependent outpatients. *Exp Clin Psychopharmacol, 13*(3), 238-243.

Helzer, J.E., Rose, G.L., Badger, G.J., Searles, J.S.,Thomas, C.S., et al. (2008). Using Interactive Voice Response to Enhance Brief Alcohol Intervention in Primary Care Settings. *J Stud Alcohol Drugs, 69,* 251-258.

Helzer, J.E., Badger, G.J., Searles, J.S., Rose, G.L., & Mongeon, J.A. (2006). Stress and alcohol consumption in heavy drinking men: Two years of daily data using Interactive Voice Response (IVR). *Alcohol Clin Exp Res, 30*, 802-811.

Herrmann, E.S., Heil, S.H., Sigmon, S.C., Dunn, K.E., Washio, Y., & Higgins, S.T. (2013). Characterizing and improving HIV/AIDS knowledge among cocaine-dependent outpatients using modified materials. *Drug Alcohol Depend, 127*(1-3), 220-225.

Higgins, S.T., Badger, G.J., & Budney, A.J. (2000b). Initial abstinence and success in achieving longer-term cocaine abstinence. *Exp Clin Psychopharmacol, 8*, 377-386.

Higgins, S.T., Budney, A.J., & Bickel, W.K. (1994a). Applying behavioral concepts and principles to the treatment of cocaine dependence. *Drug Alcohol Depend, 34*(2), 87-97.

Higgins, S.T., Budney, A.J., Bickel, W.K., Foerg, F.E., Donham, R. et al. (1994b). Incentives improve outcome in outpatient behavioral treatment of cocaine dependence. *Arch Gen Psychiatry, 51*, 568-576.

Higgins, S.T., Budney, A.J., Bickel, W.K., Hughes, J.R., Foerg, F. et al. (1993). Achieving cocaine abstinence with a behavioral approach. Am J Psychiatry, 150, 763-769.

Higgins, S.T., Delaney, D.D., Budney, A.J., Bickel, W.K., Hughes, J.R. et al. (1991). A behavioral approach to achieving initial cocaine abstinence. *Am J Psychiatry, 148*, 1218-1224

Higgins, S.T., Sigmon, S.C., Wong, C.J., Heil, S.H., Badger, G.J. et al. (2003). Community reinforcement therapy for cocaine-dependent outpatients. *Arch Gen Psychiatry, 60*, 1043-1052. (PMID: 14557150)

Higgins, S.T., Silverman, K., Sigmon, S.C., & Naito, N.A. (2012a). Incentives and health: An introduction. *Prev Med, 55*, 2-6.

Higgins, S.T., Stitzer, M.L., Bigelow, G.E., & Liebson, I.A. (1986). Contingent methadone delivery: Effects on illicit opiate use. *Drug Alcohol Depend, 17*, 311-322.

Higgins, S.T., Stitzer, M.L., McCaul, M.E., Bigelow, G.E., & Liebson, I.A. (1985). Pupillary response to a methadone challenge in chronic heroin users. *Clin Pharmacol Ther, 37*, 460-463.

Higgins, S.T., Washio, Y., Heil, S.H., Solomon, L.J., Gaalema, D.E. et al. (2012b). Financial incentives for smoking cessation among pregnant and newly postpartum women. *Prev Med, 55*, 33-40.

Higgins, S.T., Heil, S.H., Dantona, R., Donham, R., Matthews, M. et al. (2007). Effects of varying the monetary value of voucher-based incentives on abstinence achieved during and following treatment among cocaine-dependent outpatients. *Addiction, 102*(2), 271-281.

Hser, Y.I., Hoffman, V., Grella, C.E. & Anglin, M.D. (2001). A 33-year follow-up of narcotic addicts. *Arch Gen Psychiatry, 58*(5):503-508.

Hser, Y.I., Maglione, M., Polinsky, M.L., & Anglin, M.D. (1998). Predicting drug treatment entry among treatment-seeking individuals. *J Subst Ab Treat, 15*(3), 213-220.

Institute of Medicine (IOM). (1995). In R. A. Retting, & A. Yarmolinsky (Eds.) Federal regulation of methadone treatment. Washington, DC: National Academy Press.

Jasinski, D.R., Pevnick, J.S., & Griffith, J.D. (1978). Human pharmacology and abuse potential of the analgesic buprenorphine. *Arch. Gen. Psychiatry 35*, 501–516.

Johanson, C.E., Arfken, C.L., di Menza, S., & Schuster, C.R. (2012). Diversion and abuse of buprenorphine: Findings from national surveys of treatment patients and physicians. 120(1-3):190-195.

Johnson, R.E., Chutaupe, M.A., Strain, E.C., Walsh, S.L., Stitzer, M.L. et al.(2000). A comparison of levomethadyl acetate, buprenorphine, and methadone for opioid dependence. *N Engl J Med, 343*(18):1290-1297.

Johnson, R.E., Strain, E.C., & Amass, L. (2003). Buprenorphine: How to use it right. *Drug Alcohol Depend, 70*, S59-S77.

Jones, H.E., Kaltenbach, K., Heil, S.H., Stine, S.M., Coyle, M.G. et al. (2010). Neonatal abstinence syndrome following methadone or buprenorphine exposure. *N Engl J Med, 363*, 2320-2331.

Kaplan, E. H., & Johri, M. (2000). Treatment on Demand: An Operational Model. *Health Care Manag Sci, 3*(3): 171–83.

Keller, S., Bann, C.M., Dodd, S.L., Schein, J., Mendoza, T.R., et al. (2004). Validity of the Brief Pain Inventory for use in documenting the outcomes of patients with noncancer pain. *Clin J Pain, 20*, 309-318.

Kilpatrick, B., Howlett, M., Sedgwick, P., & Ghodse, A. H. (2000). Drug use, self report and urinalysis. *Drug Alcohol Depend, 58*(1-2), 111-116.

Kim, H., Bracha, Y., & Tipnis, A. (2007). Automated depression screening in disadvantaged pregnant women in an urban obstetric clinic. *Arch Womens Ment Health, 10*(4), 163-169.

Kissin, W., McLeod, C., et al. (2006). Experiences of a national sample of qualified addiction specialists who have and have not prescribed buprenorphine for opioid dependence. *J Addict Dis, 25*, 91−103

Larney, S., Randall, D., Gibson, A., & Degenhardt, L. (2012). The contributions of viral hepatitis and alcohol to liver-related deaths in opioid-dependent people. *Drug and Alcohol Dependence*, (epub ahead of print)

Lenardson, J., Gale, J.A. (2007). Distribution of substance abuse treatment facilities across the rural-urban continuum. U.S. Department of Health and Human Services, Federal Office of Rural Health Policy. Portland, ME. http://muskie.usm.maine.edu/Publications/rural/wp35b.pdf.

Lewis, J.W. (1985). Buprenorphine. Drug Alcohol Dep, 14, 363-372.

Luty, J., O'Gara, C., & Sessay, M. (2005). Is methadone too dangerous for opiate addiction? BMJ, 331(7529), 1352-1353.

Manno, J.E. (1986). Specimen collection and handling. NIDA Res Monogr, 73, 24-29.

McClure, E.A., Acquavita, S.P., Harding, E., & Stitzer, M.L. (2013). Utilization of communication technology by patients enrolled in substance abuse treatment. *Drug Alcohol Depend, 129*, 145-150.

McLellan, A. T., Arndt, I. O., Metzger, D. S., Woody, G. E., & O'Brien, C. P. (1993). The effects of psychosocial services in substance abuse treatment. *JAMA, 269*, 1953-1959.

McLellan, A.T., Luborsky, L., & Cacciola, J. (1985). New data from the Addiction Severity Index: Reliability and validity in three centers. *J Nerv Ment Dis, 173*, 412-423.

Meader, N. (2010). A comparison of methadone, buprenorphine and alpha(2) adrenergic agonists for opioid detoxification: A mixed treatment comparison meta-analysis. *Drug Alcohol Depend, 108*(1-2), 110-114.

Mello, N.K. & Mendelson, J.H. (1980). Buprenorphine suppresses heroin use by heroin addicts. *Science, 207*, 657–659.

Mello, N.K., Mendelson, J.H. & Kuehnle, J.C. (1982). Buprenorphine effects on heroin self-administration: an operant analysis. *J Pharmacol Exp Ther, 223*, 30–39.

Moore, B.A., Barry, D.T., Cutter, C.J., Sullivan, L.E., O'Connor, P.G., et al. (2012). Counseling and directly observed medication for primary care buprenorphine/naloxone maintenance: A pilot study. *J Addict Med, 6*:205-211.

Moore, B.A., Fazzino, T., Garnet, B., Cutter, C., & Barry, D. (2011). Computer-based interventions for drug use disorders: A systematic review. *J Subst Abuse Treat*, 40:215-223.

Moore, B.A., Fiellin, D.A., Barry, D.T., Sullivan, L.E., Chawarski, M., et al. (2007). Primary care office-based buprenorphine treatment: Comparison of heroin and prescription-opioid dependent patients. *J Gen Intern Med, 22,* 527-530.

Moore, B.A., Fazzino, T., Barry, D.T., Fiellin, D.A., Cutter, C.J., et al. (2013). The Recovery Line: A pilot trial of automated, telephone-based treatment for continued drug use in methadone maintenance. *J Subst Abuse Treat, 45*, 63-69.

Netherland, J., Botsko, M., Egan, J.E., Saxon, A.J., Cunningham, C.O., et al. (2009). Factors affecting willingness to provide buprenorphine treatment. *J Subst Abuse Treat*, 36, 244-251.

Office of National Drug Control Policy (ONDCP). (2008). Vermont drug control update. http://www.whitehouse.gov/sites/default/files/docs/state_profile_-_vermont.pdf.

Peachey, J. E. & Lei, H. (1988). Assessment of opioid dependence with naloxone. *Br J Addict, 83*(2), 193-201.

Peles, E., Schreiber, S., & Adelson, M. (2013). Opiate-dependent patients on a waiting list for methadone maintenance treatment are at high risk for mortality until treatment entry. *J Addict Med,* doi: 10.1097/ADM.0b013e318287cfc9

Peles, E., Schreiber, S., Sason, A., & Adelson, M. (2012). Long waiting period to enter methadone maintenance treatment: Relation to patient characteristics and outcome. *Eur Addict Res, 18*(3), 149-152.

Peterson, J.A., Schwartz, R.P., Mitchell, S.G., Reisinger, H.S., Kelly, S.M., et al. (2010). Why don't out-of-treatment individuals enter methadone treatment programmes? *Int J Drug Policy, 21,* 36-42.

Preston, K.L., Silverman, K., Schuster, C.R., Cone, E.J. (1997). Comparison of self-reported drug use with quantitative and qualitative urinalysis for assessment of drug use in treatment studies. *NIDA Res Monogr*, 167:130-45.

Rosado, J., Sigmon, S.C., Jones, H., Chilsolm, C., & Stitzer, M.L. (2005). Cash value of voucher reinforcers in pregnant drug-dependent women. *Exp Clin Psychopharmacol, 13*, 41-47.

Rose, G.L. Skelly, J.M., Badger, G.J., Naylor, M.R. & Helzer, J.E. (2012). Interactive Voice Response (IVR) for Relapse Prevention Following CBT for Alcohol Use Disorders: A Pilot Study. *Psychol Serv, 9*, 174-184 [Special section on technology-based mental health services].

Rose, G.L., MacLean, C.D., Skelly, J., Badger, G.J., Ferraro, T.A., et al. (2010a). Interactive voice response technology can deliver alcohol screening and brief intervention in primary care. *J Gen Intern Med, 25*(4):340-4.

Rose, G.L., Skelly, J.M., Badger, G.J., MacLean, C.D., Malgeri, M.P., et al. (2010b). Automated screening for at-risk drinking in a primary care office using interactive voice response. *J Stud Alcohol Drugs, 71,* 734-738.

Rosen, M.I., Wallace, E.A., McMahon, T.J., Pearsall, R., Woods, S.W., et al. (1994). Buprenorphine: duration of blockade of effects of intramuscular hydromorphone. *Drug Alcohol Depend, 35*, 141–149.

Rosenthal, R.N., Ling, W., Casadonte, P., Vocci, F., Bailey, G.L., Kampman, K., Patkar, A., Chavoustie, S., Sigmon, S.C., Blasey, C. & Beebe, K.L. (in prep). Buprenorphine implants for treatment of opioid dependence: Randomized comparison to placebo and sublingual buprenorphine/naloxone. *Addiction*.

Rounsaville, B.J. & Kosten, T.R. (2000). Treatment for opioid dependence: Quality and access. *JAMA*, *283*(10):1337-1339.

Schwartz, R.P., Highfield, D.A., Jaffe, J.H., Brady, J.V., Butler, C.B., et al. (2006). A randomized controlled trial of interim methadone maintenance. *Arch Gen Psychiatry, 63,* 102-109.

Schneider, M.F., Bailey, J.E., Cicero, T.J., et al. (2009). Integrating nine prescription opioid analgesics and/or four signal detection systems to summarize statewide prescription drug abuse in the United States in 2007. *Pharmacoepidemiol Drug Saf, 18(*9), 778-790.

Schwartz, R.P., Jaffe, J.H., O'Grady, K.E., Kinlock, T.W., Gordon, M.S., Kelly, S.M., et al. (2009b). Interim methadone treatment: Impact on arrests. *Drug Alcohol Depend, 103*, 148-154.

Schwartz, R.P., Jaffe, J.H., Highfield, D.A., Callaman, J.M., & O'Grady, K.E. (2007). A randomized controlled trial of interim methadone maintenance: 10-Month follow-up. *Drug Alcohol Depend, 86*, 30-36.

Schwartz, R.P., Jaffe, J.H., O'Grady, K.E., Das, B., Highfield, D.A., & Wilson, M.E. (2009a). Scaling-up interim methadone maintenance: Treatment for 1,000 heroin-addicted individuals. *J Subst Abuse Treat, 37,* 362-367.

Schwartz, R.P., Kelly, S.M., O'Grady, K.E., Gandhi, D., & Jaffe, J.H. (2011). Interim methadone treatment compared to standard methadone treatment: 4-month findings. *J Subst Ab Treat*, 41, 21-29.

Searles, J.S, Helzer, J.E., Rose, G. L., & Badger, G.J. (2002). Concurrent and retrospective reports of alcohol consumption across 30, 90, and 366 days: Interactive Voice Response compared to the Timeline Follow Back. *J Stud Alcohol, 63*, 352-362.

Secades-Villa, R., García-Rodríguez, O., García-Fernández, G., Sánchez-Hervás, E., Fernandez-Hermida, J.R., et al. (2011). Community reinforcement approach plus vouchers among cocaine-dependent outpatients: Twelve-month outcomes. *Psychol Addict Behav, 25*(1), 174-179.

Secades-Villa, R., García-Rodríguez, O., Higgins, S.T., Fernández-Hermida, J.R., & Carballo, J.L. (2008). Community reinforcement approach plus vouchers for cocaine dependence in a community setting in Spain: Six-month outcomes. *J Subst Abuse Treat, 34*(2), 202-207.

Selzer, M.L. (1971). The Michigan Alcoholism Screening Test: The quest for a new diagnostic instrument. *Am J Psychiatry, 127*, 1653-1658.

Shah, N.G., Lathrop, S.L., Reichard, R.R., & Landen, M.G. (2008). Unintentional drug overdose death trends in New Mexico, USA, 1990-2005: Combinations of heroin, cocaine, prescription opioids and alcohol. *Addiction, 103,* 126-136.

Sigmon, S.C. (2006). Characterizing the emerging population of prescription opioid abusers. *Am Journal Addict, 15* (3), 208-212.
Sigmon, S.C. (2008). Prescription drugs. In G.L. Fisher & N.A. Roget (Eds.), Encyclopedia of Substance Abuse Prevention, Treatment, and Recovery. California: Sage Publications, Inc., pp 695-698.
Sigmon, S.C. & Stitzer, M.L. (2005). Use of a low-cost incentive intervention to improve counseling attendance among methadone-maintained patients. *J Subst Abuse Treat, 29*, 253-258.
Sigmon, S.C., & Meyer, A.C. (in preparation). Utility of sustained-release buprenorphine formulations for treating opioid dependence: A web-based survey of physician opinion.
Sigmon, S.C., & Patrick, M.E. (2012). The use of financial incentives in promoting smoking cessation. *Prev Med, 55*, 24-32.
Sigmon, S.C., Bisaga, A., Nunes, E.V., O'Connor, P., Kosten, T., et al. (2012). Opioid detoxification and naltrexone induction strategies: Recommendations for clinical practice. *Am J Drug Alcohol Abuse, 38*(3), 187-99.
Sigmon, S.C., Correia, C., & Stitzer, M.L. (2004a). Cocaine abstinence during methadone maintenance: Effects of repeated exposure to voucher-based reinforcement and predictive utility for response to abstinence incentive interventions. *Exp Clin Psychopharmacol, 12*(4), 269-275.
Sigmon, S.C., Dunn, K., Saulsgiver, K., Patrick, M., Badger, G.J., et al. (2013). A randomized, double-blind evaluation of buprenorphine taper duration in primary prescription opioid abusers. *JAMA Psychiatry*. doi:10.1001/jamapsychiatry.2013.2216
Sigmon, S.C., Dunn, K.E., Badger, G.J., Heil, S.H., & Higgins, S.T. (2009). Brief buprenorphine detoxification for the treatment of prescription opioid dependence: A pilot study. *Addict Behav, 34*, 304-311.
Sigmon, S.C., Higgins, S.T. & Badger, G.J. (2000). Characterizing HIV/AIDS knowledge among cocaine-dependent outpatients. Paper presented at the 108th Annual Convention of the American Psychological Association, Washington, DC.
Sigmon, S.C., Moody, D.E., Nuwayser, E.S., & Bigelow, G.E. (2006). An injection depot formulation of buprenorphine: Extended biodelivery and effects. Addiction, 101, 420-432.
Sigmon, S.C., Patrick, M., Meyer, A.C., Heil, S.H., Badger, G.J. & Higgins, S.T. (in preparation). Maintaining smoking abstinence among patients receiving opioid agonist treatment with contingent voucher-based incentives.
Sigmon, S.C., Patrick, M.E., & Meyer, A.C. (in preparation). Characterizing barriers to ongoing opioid treatment among methadone-maintained patients in a rural state.
Sigmon, S.C., Wong, C.J., Nuwayser, E., Chausmer, A., & Bigelow, G.E. (2004b). Evaluation of depot buprenorphine: Placebo comparison. *Addiction, 99*, 1439-1449.
Sobell, L.C., Sobell, M.B., Leo, G.I., & Cancilla, A. (1988). Reliability of a timeline method: assessing normal drinkers' reports of recent drinking and a comparative evaluation across several populations. *Br J Addict, 83*, 393-402.
Sobel, B.-F.X., Sigmon, S.C., Walsh, S.L., Johnson, R.E., Liebson, I.A., et al. (2004). Open-label trial of an injection depot formulation of buprenorphine in opioid detoxification. *Drug Alc Depende, 73*, 11-22.
Stacy, J.N., Schwartz, S.M., Ershoff, D., & Shreve, M.S. (2009). Incorporating tailored interactive patient solutions using interactive voice response technology to improve statin adherence: Results of a randomized clinical trial in a managed care setting. *Popul Health Manag, 12*(5), 241-254.
Stitzer, M.L. & Sigmon, S.C. (2006). Other substance use disorders: Prevalence, consequences, detection and management. In: Strain EC, Stitzer ML, eds. *The Treatment of Opioid Dependence*. Baltimore, MD: The Johns Hopkins University Press, pp. 365-397.
Stotts, A.L., Dodrill, D.C., Kosten, T.R. (2009). Opioid dependence treatment: Options in pharmacotherapy. *Expert Opin Pharmacother, 10*(11):1727-1740.
Substance Abuse and Mental Health Services Administration (SAMHSA). (2006a). Diversion and abuse of buprenorphine: A brief assessment of emerging indictors. Final Report. http://buprenorphine.samhsa.gov/Buprenorphine_ FinalReport_12.6.06.pdf
Substance Abuse and Mental Health Services Administration (SAMHSA). (2006b). Diversion and abuse of buprenorphine: A brief assessment of emerging indictors. Results of the Vermont Case Study. http://buprenorphine.samhsa.gov /Vermont.Case.Study_12.5.06.pdf
Substance Abuse and Mental Health Services Administration. (2010). *Results from the 2009 National Survey on Drug Use and Health: Volume I. Summary of National Findings* (Office of Applied Studies, NSDUH Series H-38A, HHS Publication No. SMA 10-4856 Findings). Rockville, MD. http://oas.samhsa.gov/NSDUH/2k9NSDUH/2k9Results.htm

Sullivan, L.E., Barry, D., Moore, B.A., Chawarski, M.C., Tetrault, J.M., et al. (2006). A trial of integrated buprenorphine/naloxone and HIV clinical care. *Clin Infect Dis, 43*:S184-190.

Sullivan, L.E., Moore, B.A., Chawarski, M.C., Pantalon, M.J., Barry, D., et al. (2008). Buprenorphine/naloxone treatment in primary care is associated with decreased HIV risk behaviors. *J Subst Abuse Treat, 35*:87-92.

Tacke, U., Uosukainen, H., Kananen, M., Kontra, K., & Pentikäinen, H. (2009). A pilot study about the feasibility and cost-effectiveness of electronic compliance monitoring in substitution treatment with buprenorphine–naloxone combination. *J Opioid Manag, 5*, 321–329.

Treatment Episode Data Set (TEDS). (2004). National admissions to substance abuse treatment services: 1992-2002. DASIS Series: S-23, DHHS Publication No. (SMA) 04-3965. Rockville, MD.

Tetrault, J.M., Moore, B.A., Barry, D.T., O'Connor, P.G., Schottenfeld, R.S., et al. (2012) Brief versus extended counseling along with buprenorphine/naloxone for HIV-infected opioid dependent patients. *J Subst Abuse Treat, 43*:433-439.

Uosukainen, H., Pentikainen, H., & Tacke, U. (2013). The effect of an electronic medicine dispenser on diversion of buprenorphine-naloxone: Experience from a medium-sized Finnish city. *J Subst Ab Treat, 45,* 143-147.

Wall, T.L., Sorensen, J.L., Batki, S.L., Delucchi, K.L., London, J.A., et al. (1995). Adherence to zidovudine (AZT) among HIV-infected methadone patients: A pilot study of supervised therapy and dispensing compared to usual care. *Drug Alcohol Depend, 37*, 261-269.

Walsh, S.L., Preston, K.L., Bigelow, G.E., & Stitzer, M.L. (1995). Acute administration of buprenorphine in humans: Partial agonist and blockade effects. *J Pharmacol Exp Ther, 274*, 361-372.

Walsh, S.L., Preston, K.L., Stitzer, M.L., Cone, E.J., & Bigelow, G.E. (1994). Clinical pharmacology of buprenorphine: Ceiling effects at high doses. *Clin Pharmacol Ther, 55,* 569-580.

Warner-Smith, M., Darke, S., Lynskey, M., & Hall, W. (2001). Heroin overdose: Causes and consequences. *Addiction, 96*, 1113–1125.

Weiss, R.D., Potter, J.S., Provost, S.E., et al. (2010). A multi-site, two-phase, prescription opioid addiction treatment study (POATS): Rationale, design, and methodology. *Contemp Clin Trials, 31*(2), 189-199.

Wenger, L. D., & Rosenbaum, M. (1994). Drug treatment on demand – not. *J Psychoactive Drugs, 26,* 1−11.

Wish, E.D., Hoffman, J.A., & Nemes, S. (1997). The validity of self-reports of drug use at treatment admission and at followup: Comparisons with urinalysis and hair assays. *NIDA Res Monogr, 167*, 200-226.

Wisniewski, A.M., Purdy, C.H., & Blondell, R.D. (2008). The epidemiologic association between opioid prescribing, non-medical use, and emergency department visits. *J Addict Dis, 27*, 1-11.

Yancovitz, S.R., Des Jarlais, D.C., Peyser, N.P., Drew, E., Friedmann, et al. (1991). A randomized trial of an interim methadone maintenance clinic. *Am J PubHealth, 81,* 1185-1191.

Yoon, J.H., & Higgins, S.T. (2008). Turning k on its head: Comments on use of an ED50 in delay discounting research. *Drug Alcohol Depend, 95*, 169-172.

CHRMS 14-063 Final Protocol:
Interim Treatment: Leveraging buprenorphine + technology to bridge waitlist delays
Principal Investigator: Stacey Sigmon, Ph.D.

Summary of changes between original and final protocols:

- added piloting of an initial 10-15 subjects in the full IBT condition to finalize all procedural details before proceeding with randomized trial to assist with treatment development
- added a brief, anonymous Lime Survey to deliver to treatment providers in Vermont to solicit their opinions about the utility/value of IBT treatment components to assist with treatment development
- added an IVR phone-based system for providing basic support and monitoring and for automating random call-backs
- added an iPad-based HIV & hepatitis educational intervention
- added two additional follow-up assessment at (post-study) 36 and 48 weeks
- discontinued the originally-proposed post-study optional 4-week taper as it is more appropriate for opioid-dependent to transition to continued maintenance in community clinics post-study than detoxification

STUDY PROTOCOL

Interim Treatment: Leveraging buprenorphine + technology to bridge waitlist delays

Principal Investigator: Stacey Sigmon, Ph.D.

INTRODUCTION

Opioid abuse is a significant national and international public health problem (European Monitoring Centre for Drugs and Drug Addiction, 2010; SAMHSA, 2010a). Opioid-related consequences include emergency department visits, drug overdoses, premature death, criminal activity, lost workdays and economic costs that in the U.S. exceed $56 billion annually (Becker et al., 2008; Birnbaum et al., 2011; Clausen et al., 2009; Hser et al. 2001; Shah et al., 2008; Wisniewski et al., 2008). Agonist maintenance is the most efficacious treatment for opioid dependence and dramatically reduces morbidity, mortality and spread of infectious disease (Ball & Ross, 1991; Johnson et al., 2000; Stotts et al., 2009). However, demand for treatment far exceeds available capacity (Friedmann et al., 2003; Wenger & Rosenbaum, 1994). Due to inadequate public funding, unfavorable zoning regulations and requirements for comprehensive care in programs that increase their cost, an alarming number of methadone clinics nationally and internationally have extensive waitlists (Des Jarlais et al., 1995; Fountain et al., 2000; Gryczynski et al., 2009; Peles et al., 2012, 2013; Peterson et al., 2010). Barriers to treatment access are not limited to methadone clinics. While approval of office-based BUP treatment extended agonist maintenance into general medical practices, many areas of the country have an insufficient number of willing providers, in part due to physicians' concerns about induction logistics, reimbursement challenges, potential for medication diversion, lack of support for providers and lack of psychosocial services for patients (Barry et al., 2008; Becker & Fiellin, 2006; Kissin et al., 2006; Netherland et al., 2009). The result is that opioid-dependent patients can remain on waitlists for years and are at significant risk for illicit drug use, criminal activity, infectious disease, overdose and mortality during this delay to treatment (Adamson & Sellman, 1998; Clausen et al., 2009; Cooper, 1989; Darke & Hall, 2003; Schwartz et al., 2009; Warner-Smith et al., 2001; Wenger & Rosenbaum, 1994). Prolonged waits are also associated with reduced likelihood of treatment entry (Donovan et al., 2001; Festinger et al., 1995; Hser et al., 1998; Kaplan & Johri, 2000).

This represents a serious barrier to the widespread delivery of effective treatment for opioid dependence. While many geographic areas have experienced a persistent shortage in opioid-substitution treatment availability, particularly for patients who must wait for admission to a subsidized program (Schwartz et al., 2009, 2011), this problem is especially urgent in rural areas struggling with high rates of prescription opioid (PO) abuse and relatively few treatment options (Fortney & Booth, 2001; Lenardson & Gale, 2007; Rosenblum et al., 2011; Rounsaville & Kosten, 2000). In Vermont, for example, rates of PO abuse are among the highest in the country (TEDS, 2004; ONDCP, 2008; Schneider et al., 2009), yet our state's primary methadone service (for which Dr. Sigmon is Director) has a waiting list of 823 people and 1.5 years. Further, while Vermont is among the leaders in the country in per capita number of BUP providers (SAMHSA, 2006ab), the vast majority are willing to treat only a handful of patients and thus it is extremely difficult for individuals to find an available provider (Department of Vermont Health Access, 2012). A similar scenario is seen in other rural states. In Kentucky, for example, the public methadone clinic in Lexington has an average 2-year wait for treatment slots (M. Lofwall, University of Kentucky, personal communication).

One important effort to increase access to opioid treatment has been to offer interim methadone treatment (IMT) to those awaiting enrollment into a methadone program. In this paradigm, approved methadone clinics can provide medication without accompanying psychosocial services on a temporary basis when only a waiting list would be otherwise available (IOM, 1995). IMT reduces drug use and drug-related risk behaviors during the prolonged wait for treatment access (Gruber et al., 2008; Schwartz et al., 2006, 2007, 2008, 2009a,b, 2011; Yancovitz et al., 1991). In the first experimental investigation, for example, 319 heroin-dependent participants were randomly assigned to IMT (n=199) or a waiting list control (n=120; Schwartz et al., 2006). Compared to waitlist controls, IMT participants provided significantly fewer heroin-positive urines, reported greater reductions in illegal activity and were more likely to eventually enter methadone treatment. In brief, providing IMT as opposed to a waitlist when a formal treatment slot is not readily available reduces drug-related risks and costs to the patient and for society more generally.

Despite these promising outcomes, methadone's regulatory and pharmacological features constrain the ability of IMT to significantly expand access to much-needed treatment. Methadone treatment in the U.S. is

limited to licensed specialty clinics, it requires frequent clinic visits, and the medication itself has risks of diversion, abuse and overdose (Luty et al., 2005). IMT regulations mandate that patients ingest all doses under direct observation, thus requiring daily clinic visits (IOM, 1995). They also limit the duration of IMT to no more than 120 days, with clinics required to discharge patients at that time or admit them to standard methadone treatment if a slot has become available. These constraints are incompatible with an environment of already-constrained resources and severely limit the ability of IMT to increase treatment access.

Our overarching goal is to develop a novel Interim Buprenorphine Treatment (IBT) that can bridge delays in access to life-saving treatment. Our integrative treatment package includes three key components, each strategically chosen to maximize patient access to efficacious medication while minimizing risk of nonadherence, abuse and diversion:

(1) Buprenorphine. The partial opioid agonist buprenorphine (BUP) was approved by the FDA in 2002 for the treatment of opioid dependence and exhibits a pharmacological profile that offers several advantages over other medications for treating opioid dependence (Bickel & Amass, 1995; Johnson et al., 2003). A ceiling on its agonist activity may reduce abuse liability and contribute to a superior safety profile (Banks, 1979; Jasinski et al., 1978; Lewis, 1985; Mello & Mendelson, 1980; Walsh et al., 1994, 1995). BUP also attenuates the effects of other opioids, thus suppressing illicit use during treatment (Bickel et al., 1988; Jasinski et al., 1978; Mello & Mendelson, 1980; Mello et al., 1982; Rosen et al., 1994; Walsh et al., 1995). Finally, BUP is available without the rigid dosing regulations and 120-day interim-dosing limit required for methadone. Taken together, BUP is uniquely compatible with an interim-dosing approach to treating opioid dependence.

Despite this impressive set of therapeutic features, only a single study has evaluated BUP's utility in an interim treatment paradigm. That trial was conducted in Oslo, Norway over a decade ago with 106 heroin-dependent individuals awaiting methadone treatment (Krook et al., 2002). Participants were randomized to receive BUP (n=55) or placebo (n=51) for 12 weeks, without psychosocial support. BUP was associated with significantly greater retention (Figure 1), with BUP and placebo participants retained for 42 vs. 14 days, respectively. Self-reported heroin use, assessed via a visual analogue scale ranging from 0 (Drug Free) to 10 (Daily Heavy Drug Abuse), was also significantly lower in the BUP vs. placebo group (Figure 2).

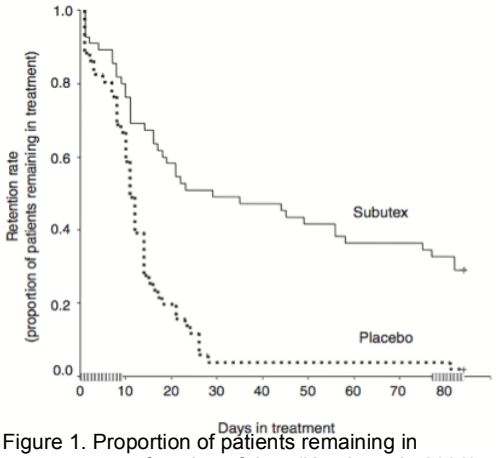

Figure 1. Proportion of patients remaining in treatment as a function of time (Krook et al., 2002)

Though this study provided encouraging initial support for BUP's role in interim treatment, it suffered from several important methodological limitations. While the BUP group demonstrated superior retention, attrition was still high with two-thirds of patients having dropped out by Week 12. The authors also used no objective measure of opioid abstinence, relying instead on patients to rate their recent opioid use via visual analogue scales. Finally, the study required near-daily clinic visits (Monday-Saturday) for observed dosing, which still translates to a resource-intensive treatment that fails to capitalize on BUP's favorable pharmacological profile.

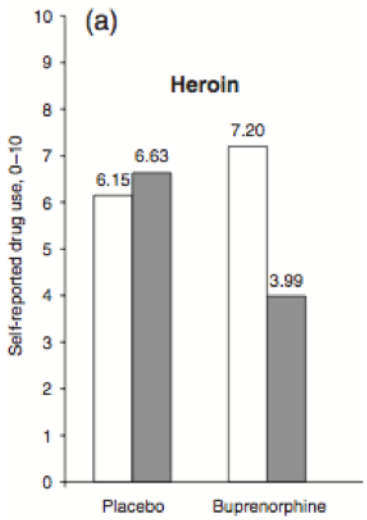

Figure 2. Self-reported severity of heroin use via VAS at baseline (open bars) and during entire 12-week study (filled bars)(Krook et al., 2002)

We propose that a thoughtfully developed treatment package that integrates BUP with innovative technology-based components can produce an IBT that truly expands treatment access while minimizing nonadherence and eliminating the need for daily visits. Below we describe the additional components that we will strategically combine to create this novel IBT protocol.

(2) Computerized adherence monitoring. While BUP's pharmacological profile makes it an excellent fit with an interim dosing arrangement, concerns about possible nonadherence, abuse or diversion could limit its widespread use in clinical settings (Fiellin et al., 2006; Johanson et al., 2012; Sigmon et al., 2004). Thus, the proposed IBT intervention will use computerized adherence monitoring (CAM) to promote adherence and minimize risk of diversion. Electronic medication dispensers have been used for many years to monitor and improve adherence in clinical populations in whom compliance is often poor, particularly antiretroviral therapy adherence among HIV-positive patients with concurrent substance abuse or

psychiatric illness (e.g., Arnsten et al., 2001; Badiee et al., 2012; Wall et al., 1995). These studies have typically used computerized caps placed on prescription bottles (e.g., Medication Event Monitoring System (MEMS), Aprex Corporation, Fremont, CA). Patients are instructed to remove only one dose at a time and to use only the MEMS bottle to dispense their medication. The cap contains a microprocessor that records the date and time of each opening. Only one study has used MEMS caps in BUP treatment, though not as its primary focus (Fiellin et al., 2006). That trial sought to compare varying intensities of counseling and medication monitoring in patients receiving BUP maintenance in primary care. Patients attended the clinic once vs. thrice weekly, received their remaining doses in pill bottles with MEMS caps, and were considered adherent for a given day if there was a recording of the bottle having been opened. BUP adherence was moderate (71% of study days), varied widely across patients, and was significantly correlated with illicit opioid abstinence. The authors concluded that this variability highlights the need to measure BUP adherence in future research and to monitor and encourage adherence in clinical practice to improve treatment outcomes.

While MEMS caps offer important benefits, they also have substantive limitations. The pill bottle given to patients contains all of the doses for the given period (e.g., week or month) and thus patients have access to the entire prescription each time they open it. Additionally, the cap only records a time-date stamp for each opening rather than the number of pills removed. A patient could, therefore, remove more than the prescribed amount at one time, replacing it with illicitly-obtained medication at a subsequent opening if s/he is called in for a pill count. This issue is especially important when dealing with pharmacotherapies for opioid dependence. That is, while the primary concern with HIV-positive patients is that they will simply fail to take their medication, with opioids there is the additional serious concern regarding potential for abuse (e.g., taking more than prescribed) or diversion (e.g., sharing or selling doses) of medication.

An important and exciting advance is the recent development of portable, disk-shaped devices that hold multiple-day doses across separate secure cells. The Med-O-Wheel Secure device, for example, accommodates doses for up to 28 days, with each day's dose secured in its own locked compartment around the dosage cassette (Addoz, Forssa, Finland; Figure 3). Each day's dose is available for a 3-hour window around a predetermined dosing time, during which the patient can press a button to prompt the appropriate compartment to move into an accessible position. Once this time window has ended, the device transitions into a "closed" mode automatically and tablets become inaccessible until the next preset time. It also includes locks and alarms to prevent tampering and access to tablets outside the preset time window. The Med-O-Wheel has begun to be used clinically in Finland in the hopes of reducing the general availability of illegal BUP, with recent reports noting favorable feasibility and acceptance by patients and staff (Tacke et al., 2009; Uosukainen et al., 2013). However, to our knowledge, the proposed study would be the first to directly evaluate this device as a component of BUP treatment for opioid dependence.

Figure 3.

(3) *m*Health clinical support platform. Though there is evidence that opioid treatment outcomes may be enhanced by increasing the intensity of psychosocial services (e.g., McLellan et al., 1993), an intensive clinical support package is impractical for the resource-constrained settings in which interim treatments are delivered. One alternative is the rapidly-expanding use of mobile health (*m*Health) platforms for healthcare research and delivery, particularly as an increasing number of devices offer portable technology with sophisticated computational methods (Boyer et al., 2010). *m*Health applications hold significant promise for extending the reach of health care by permitting delivery of monitoring, education, point-of-care diagnostics and even evidence-based treatments beyond the confines of the medical office. Interactive Voice Response (IVR) systems are particularly promising in that they provide customized content and support via phone and offer advantages of low cost, consistent delivery, expanded access, 24-hour availability, privacy and convenience (Crawford et al., 2005; Helzer, Rose et al., 2008; Kim et al., 2007; Moore et al., 2013; Rose et al., 2010; Stacy et al., 2009). IVR systems can accommodate complex branching logic for follow-up interview questions or other messages in a seamless fashion that is transparent to the user. Patients typically use keypad or voice responses to choose among menu options, respond to prompts and answer questions. While early studies typically used IVR to provide basic support (e.g., patient reminders, brief assessments, self-monitoring prompts), recent studies have included more sophisticated, therapeutic components such as goal setting and coping skills rehearsal. Much of the seminal IVR research with substance use disorders was conducted by our UVM colleagues, Drs. Rose and Helzer, in studies of automated interventions for alcohol abuse in primary care settings (Helzer, Rose et al., 2008; Rose et al., 2010ab).

Importantly, IVR systems are uniquely compatible with IBT and the opioid-dependent population. They are an excellent fit with resource-constrained settings, requiring no specialized equipment or extensive training. IVR hardware and software can support multiple clinic sites and have no on-site installation costs beyond telephone access. IVR systems provide broad access for lower income and marginalized populations, as touch-tone phones are familiar, easy to use, and more widely available than computers. They use an auditory interactive process that is not hampered by low literacy. Privacy and anonymity are also greater than on a computer screen or written questionnaire as others cannot see or hear the questions or responses.

Despite this, we know of only one published study evaluating IVR with opioid-dependent patients. In that recent pilot trial, Moore and colleagues (2013) evaluated the feasibility and acceptability of a therapeutic IVR system in 36 methadone-maintained patients who continued to use illicit drugs during treatment. Patients were randomized to receive treatment-as-usual (TAU) or TAU+Recovery Line (RL) for 4 weeks. The RL was based on a cognitive behavioral therapy framework and included brief modules on a range of topics (e.g., self-monitoring, coping with craving, managing high-risk situations, mood and stress). TAU+RL participants had 24-hour IVR access and could call in at any time to complete modules. Patients' ratings of the RL were high and they were more likely to report opioid and cocaine abstinence on days they used the RL than on days they did not. Data from this initial pilot study suggested that IVR was acceptable and feasible for use with methadone patients.

We propose to develop an *m*Health platform that is compatible with a low-intensity, extended-reach IBT approach among opioid-dependent individuals awaiting treatment. The automated IVR system will assess drug use and provide customized monitoring throughout the IBT period. It will include branching logic that provides follow-up questions, messages and information, as well as immediate connection with staff if needed. We will program the system to automatically contact participants each day rather than participants having to call into the system, which will further support IVR utilization by patients during IBT.

(4) Urinalysis and adherence monitoring. Biochemical verification, typically via urine toxicology, is the most accurate and objective method for evaluating recent drug use (Chermack et al., 2000; Fendrich et al., 2004; Kilpatrick et al., 2000; Preston et al., 1997; Wish et al., 1997). Our long-standing protocol with illicit drug abusers involves thrice-weekly urinalysis (UA) monitoring during the early months of treatment (e.g., Sigmon et al., in press; Higgins, Sigmon et al., 2003), often followed by a reduction to twice weekly once patients are stable in treatment. The patient provides a specimen under staff observation which first undergoes validity testing (e.g., appropriate temperature and concentration, no adulterants present). It is analyzed on-site via enzyme multiplied immunoassay (Microgenics, Fremont, CA) for the primary drug (e.g., opioids). One randomly-selected sample each week is also analyzed for other illicit drugs (e.g., cocaine, amphetamines, benzodiazepines, marijuana, barbiturates). Taken together, these features produce a rigorous UA monitoring protocol with a high likelihood of detecting even low levels of drug use.

While higher-frequency monitoring maximizes detection of drug use (Cone & Dickerson, 1992), thrice-weekly visits are incompatible with IBT specifically and with resource-constrained settings more generally. To balance the rigor of the above UA procedure with the less-intensive schedule necessary for IBT, we will develop a UA protocol that utilizes a random sampling approach. In this arrangement, patients are contacted at random times and instructed to visit the clinic for urine testing (Manno, 1986). Random sampling increases the effectiveness of UA monitoring, as patients are always in the position of not knowing when the next screen will be requested, reducing the possibility that s/he can tailor drug use to subvert monitoring (e.g., discontinue use long enough prior to a scheduled visit to test negative; Harford & Kleber, 1978).

We will develop a novel call-back program that will contact participants via IVR on a schedule generated using a computerized random number algorithm. The participant will be instructed to return to the clinic within approximately 12 hrs to provide a staff-observed urine specimen. They will also present their CAM device for inspection by staff to further ensure there is no evidence of tampering, nonadherence or diversion. This protocolized component will provide a rigorous yet efficient approach for supporting abstinence and adherence over an extended period of lower-frequency clinic visits.

(5) HIV+Hepatitis Education. While IBT is intended as a low-intensity, extended-reach paradigm, we believe it is essential to include an evidence-based intervention to enhance HIV and hepatitis knowledge in opioid abusers awaiting treatment. In the U.S., HIV and hepatitis are responsible for an estimated 14,299 (CDC, 2011) and 15,768 (CDC, 2008) annual deaths, respectively, and deaths from hepatitis-related liver complications are increasing among opioid abusers (Larney et al., 2012). Thus, efforts to reduce disease transmission in this population are vital. Brief psychosocial interventions that focus on increasing knowledge about disease prevention and infection are appealing in that they can be done within a single session, do not require specialized counselor training and have been associated with a decrease in self-reported risk

behaviors in two recent reviews (Copenhaver et al., 2006; Meader et al., 2010). Our team has developed a single-visit intervention that produces significant improvements in HIV knowledge and reductions in self-reported risk behaviors in cocaine-dependent outpatients (Heil et al., 2005; Herrmann et al., 2013). In our BUP trial with PO abusers (Sigmon et al., in press), we expanded the intervention to also include information on hepatitis and to emphasize noninjection risk behaviors in opioid-dependent patients. The intervention produced significant increases in both HIV and hepatitis knowledge (Figure 5; Dunn et al., 2013).

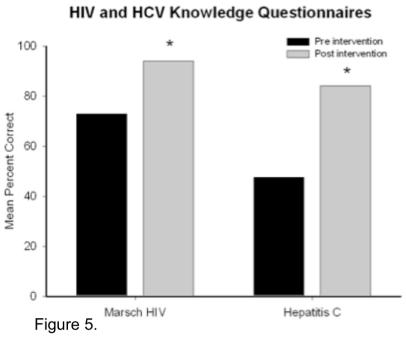

Figure 5.

These studies demonstrate that this single-visit intervention produces substantial gains in HIV and hepatitis knowledge in illicit drug abusers. However it has typically been delivered in a resource-intensive, in-person format, which may limit its utility in an interim dosing protocol. **Thus, we propose to adapt our evidence-based HIV+Hepatitis Education intervention for delivery via an iPad platform, a state-of-the-art mobile device with portability, sophisticated functionality and widespread appeal.**

Summary

Despite the undisputed effectiveness of agonist maintenance for opioid dependence, current capacity is inadequate to meet demand in the U.S. and internationally. There is a critical need to develop new and creative approaches for bridging gaps in treatment access. In this pilot study, we propose to develop an integrative interim BUP treatment that will increase access to pharmacotherapy for opioid dependence while reducing risk of nonadherence, abuse and diversion by leveraging state-of-the-art technology and rigorous, evidence-based methodology to verify protocol adherence. The overarching goal and specific aims of the project are directly relevant to our mission of improving the accessibility, implementation and effectiveness of drug abuse treatment.

INNOVATION

This project is highly innovative in at least four important ways: **(1)** By facilitating the eradication of waitlists for opioid treatment, this research represents a significant departure from the status quo and stands to produce a fundamental shift in how treatment of opioid dependence is conceptualized and delivered. **(2)** Our use of BUP is also a novel feature of the proposed study, as it will be the first to rigorously integrate a medication with fewer regulatory and pharmacological constraints into an integrative interim treatment model to mitigate delays in treatment access. **(3)** We propose to develop one completely novel treatment components (i.e., random call-back algorithm for UA and adherence monitoring) for this project. We also will refine three additional components (i.e., interim BUP dosing, CAM) in ways that will significantly enhance their disseminability. The development and/or refinement of each of these features individually will represent an important and innovative methodological advance in this area of research. Further, the unique combination of these components will produce an integrative treatment package for opioid dependence that is entirely novel. **(4)** The proposed research will extend our scientific knowledge about interim agonist treatment to new populations and new settings. First, all prior studies on interim opioid treatment have been with heroin-dependent patients (Krook et al., 2002; Schwartz et al., 2006, 2007, 2009, 2011). While we will not explicitly exclude heroin users, we know from our waitlist data that the majority of participants will be primary PO abusers (70% vs. 30% endorse a PO vs. heroin, respectively, as their primary drug). Thus, this study will be the first to evaluate the feasibility and efficacy of interim dosing in primary PO abusers. Second, the prior interim treatment studies were conducted in predominantly urban areas (i.e., Baltimore; Oslo, Norway). This study will be the first to investigate the utility of IBT in the rural and suburban areas that stand to significantly benefit from it.

APPROACH

Preliminary Studies

Successful completion of this project will require access to opioid-dependent individuals, expertise in conducting opioid research and experience with the IBT components proposed. Below we describe how our team has the requisite expertise necessary to expeditiously conduct the research as proposed.

Access to opioid-dependent patients. We have ready access to the patients who stand to benefit most from IBT- that is, opioid-dependent individuals who experience significant economic and geographic barriers to treatment access. Dr. Sigmon is the Director of the first and largest opioid treatment program in Vermont, which is contiguous with our research clinics. The Chittenden Center (CC) opened in 2002, providing methadone to 50 patients. Under Dr. Sigmon's leadership, it has steadily grown over the past decade to now treat 470 patients and offer BUP in addition to methadone. Unfortunately, we also have 667 people currently on the clinic's waitlist. Of note, 68% of waitlisted individuals have Medicaid and 10% have no insurance,

making this clinic's state-subsidized treatment slots their most likely (and often only) option for treatment. Also worth noting is that barriers to treatment access are not limited to those on waitlists. In a survey of *enrolled* CC patients, patients reported that their travel distance and time to and from the clinic was approximately 21.4 miles and 60 minutes, respectively, with 85% of patients having to visit the clinic daily and 40% relying on public transportation (Sigmon et al., in prep). Patients reported spending $48.84 per week on transportation-related costs to attend the clinic. A substantial number also reported missing ≥1 clinic visit and dose due to transportation- (23%), weather- (17%) or cost-related (8%) reasons. Finally, 22% of patients reported that travel time had interfered with their ability to maintain employment. These data highlight the potential for using IBT components to also support treatment engagement among already-enrolled patients. In summary, we have access to and familiarity with the patients likely to benefit substantially from IBT, further supporting the generality of the proposed research to the larger population of opioid abusers awaiting treatment.

Expertise in opioid research. Our team has extensive experience conducting opioid research. One recent example is Dr. Sigmon's NIDA-funded R01 randomized controlled trial (RCT) examining the relative efficacy of BUP taper durations in prescription opioid (PO) abusers, which was recently published in *JAMA Psychiatry* (Sigmon et al., 2013). While agonist maintenance is the recommended treatment for most opioid-dependent patients, detoxification represents an important treatment option particularly in areas where access to maintenance is limited. We aimed to develop an outpatient detoxification protocol that surmounts the problems with attrition and relapse that typically plague such treatments. Following brief BUP stabilization, 70 PO-dependent adults were randomized to receive a 1-, 2- or 4-week taper followed by naltrexone. All received individualized behavior therapy and thrice-weekly UA monitoring. Opioid abstinence, retention and naltrexone ingestion were significantly greater in the 4- vs. 2- and 1-week conditions, suggesting that a meaningful subset of PO abusers may respond positively to a 4-week BUP taper+naltrexone treatment. Dr. Sigmon has also evaluated the safety, pharmacokinetics and efficacy of novel, sustained-release BUP formulations. This includes the first-in-human evaluations of a depot BUP formulation, which suppressed withdrawal and attenuated hydromorphone challenge for 4-6 weeks following a single administration (Sigmon et al., 2004b, 2006; Sobel et al., 2004). She also was site PI on trials evaluating a BUP implant that produces steady-state blood levels for 6 months (Beebe et al., 2012; Rosenthall et al., in prep).

We are also experienced in conducting research in the context of opioid-replacement clinics more generally. Dr. Sigmon has a NIDA R01 to develop an efficacious smoking cessation treatment for methadone- and BUP-maintained smokers and has completed a series of RCTs demonstrating its efficacy (Dunn et al., 2008, 2010; Sigmon & Patrick, 2012; Sigmon et al., in prep). She has conducted studies targeting cocaine use, counseling attendance and other clinical issues among methadone patients (Correia et al., 2005; Dunn et al., 2008, 2009; Rosado et al., 2005; Sigmon et al., 2004a; Sigmon & Stitzer, 2005; Stitzer & Sigmon, 2006). We have published numerous papers on the topic of opioid dependence more broadly, including efforts to better characterize PO abusers, to compare urban vs. rural opioid abusers and to guide physicians in the clinical management of opioid withdrawal and detoxification (Dunn et al., 2011, in prep; Heil et al., 2008; Sigmon, 2006, 2008; Sigmon et al., 2012, in prep). Finally, Dr. Sigmon is committed to expanding much-needed access to opioid treatment nationally and served as a collaborator with Dr. Charles Schuster on the Postmarketing Surveillance Project for Suboxone. On the state level, Dr. Sigmon serves on advisory boards to improve opioid treatment throughout Vermont (e.g., Prescription Monitoring Program, Committee to Revise the Vermont BUP Treatment Guidelines, Committee to Develop a Hub & Spoke BUP Treatment System).

Treatment Development Procedures

There are two general approaches to treatment development: an additive model wherein efficacious components are gradually assembled across trials and a dismantling approach wherein the aim is to develop an initially efficacious package that can then be programmatically dismantled following efficacy testing. We prefer the latter when dealing with major public health challenges because it maximizes the probability of producing an intervention that has a clinically-meaningful impact, after which we can work backwards to identify the contribution of individual elements to that effect. In contrast, with the additive model, you are more likely to be working with small or negative outcomes as you sort through the individual components for a problem that is likely to eventually need a multi-element intervention to achieve clinically meaningful outcomes. Thus, in this Stage I Behavioral and Integrative Treatment Development project, our focus will be on developing a multi-element intervention that has high likelihood of impacting the substantial problem of untreated opioid dependence. If our IBT package is shown to have initial efficacy in this pilot study and a subsequent full RCT, it will merit subsequent dismantling. Note that we (a) successfully used a similar approach to developing the CRA + Vouchers treatment for cocaine dependence that we then subsequently and programmatically dismantled into its active elements and (b) are currently having good initial success with

a package for promoting medically-approved contraceptive use in drug dependent women in an R34 through the Behavioral & Integrative Treatment Development Program.

To ensure that our process is informed by real-world providers, we will distribute a voluntary brief web-based survey in Month 1 to staff in opioid treatment programs and BUP providers to identify features they regard as necessary in an effective IBT package. We will use LimeSurvey, a web-based interface supported by UVM for the administration of online surveys that offers branching logic, flexible question formats, anonymity, mutiple output formats and graphical data displays. We will prioritize programs that are currently waitlisting patients, in order to ensure that treatment development is informed by the needs being encountered in resource-constrained clinical settings.

In Months 1-4, we will refine the IBT components, with this process informed by what we learn in our Lime Survey. Our next step will be to pilot test and make any adjustments indicated to be necessary. We will recruit 10-15 pilot participants who will receive the IBT outlined below. Based on our prior experience developing treatments for cocaine, opioid and tobacco dependence, we are confident that the proposed piloting will be sufficient for problem-solving any procedural issues with IBT components. Once piloting is complete, we will conduct a small but focused randomized study to gather initial information on efficacy (see below) and develop an IBT treatment manual to support future dissemination.

Overview of Proposed Pilot Study

In this randomized trial, opioid-dependent adults currently awaiting agonist maintenance will be randomly assigned to (1) **Interim Buprenorphine Treatment** (IBT) or (2) a **Waitlist Control** (WLC). IBT participants will complete BUP induction in Week 1 (or longer if required), during which they will attend the clinic daily. Thereafter, during Weeks 2-12 IBT participants will visit the clinic every two weeks to ingest their BUP dose, provide a urine specimen and receive their remaining doses in the Med-O-Wheel. WLC participants will remain on the waitlist for their treatment of choice. Participants in both conditions will complete follow-up assessments and provide a urine specimen at 4, 8, 12, 16, 20, 24, 36 and 48 weeks after trial entry. WLC participants who have not entered treatment by Week 12 will be offered IBT at that time, providing an additional within-subject evaluation of IBT effects. Thus the overall possible study duration (excluding follow-up assessments) may vary between 12 - 24 weeks. For example, participation will be 12 weeks for those participants randomly assigned to the 12-week IBT condition. It would be 24 weeks for WLC participants who opt, at the end of their initial 12-week waitlist condition, to receive 12 weeks of IBT.

Treatment conditions will be compared on the primary outcomes of illicit opioid abstinence and psychosocial functioning (i.e., ASI subscale scores) at each during-treatment assessment. We hypothesize that IBT participants will demonstrate reduced illicit opioid use and criminal behavior compared to WLC participants. Among WLC participants who cross over to IBT at Week 12, we hypothesize that illicit opioid use and frequency of criminal behavior will be lower during their IBT vs. waitlist phase. Secondary IBT-specific outcomes will include feasibility, acceptability, BUP adherence, retention, other drug use and patient satisfaction.

Participants. The proposed study will be conducted in the UVM Buprenorphine Research Clinic, which has been the site of BUP research for 25 years. The clinic is contiguous with our other research clinics as well as our methadone clinic for which Dr. Sigmon is Director. Participants will be 70 opioid-dependent individuals who will be assigned randomly to IBT or WLC. The primary referral source will be an IRB-approved flyer given to all CC waitlist individuals. We can also circulate ads in the larger community to reach additional patients on wait lists for treatment. Additional sources will include the Vermont State Alcohol and Drug Abuse Office, physicians, local mental health centers, a toll-free number, public service announcements, advertisements in local and alternative newspapers and flyers placed throughout the community. We have used these sources in prior studies and anticipate no difficulties gaining access to the sample needed for this trial (Dunn et al., 2008, 2010; Sigmon et al., 2009, 2013, in prep).

For inclusion in the trial, participants must be $\geq$18 years old, in good health, meet DSM-IV criteria for opioid dependence, provide an opioid-positive urine and be currently waitlisted. To minimize disruption due to treatment becoming available during the study, we will limit enrollment to those who joined a waitlist in the prior 12 months. As 349 of the CC waitlist had been added in the past 12 months (29 per month), we do not expect this criterion to impede recruitment. Those with a significant psychiatric or medical illness that may interfere with consent or participation will be excluded, as will those who are pregnant or nursing. Females will be tested for pregnancy and, should a participant become pregnant during the trial, her participation will be terminated and she will be assisted with accessing treatment at the high-risk pregnancy clinic. Those dependent on sedative-hypnotics will be excluded, due to the medical risks and notably low success rates with sedative-

dependent opioid abusers (Stitzer & Chutuape, 1999). Participants must provide written informed consent to participate. Those meeting the above criteria and interested in IBT will be eligible to participate.

Eligible participants will be randomly assigned to one of two 12-week treatment conditions: (1) Interim Buprenorphine Treatment (IBT; n=35) or (2) a Waitlist Control (WLC; n=35). Minimum likelihood allocation (Aickin, 1982) will be used to achieve balance between treatment groups on the characteristics likely to influence treatment outcomes. Stratification variables will include duration of time on waiting list, amount of opioids used per day, any past-month cocaine use, type of opioid (heroin vs. prescription opioid) and lifetime history of IV use.

Assessments. Participants will complete an intake assessment that includes: a drug history questionnaire developed by our clinic; the Addiction Severity Index (ASI; McLellan et al., 1985); the psychoactive substance abuse disorder sections of the DSM-IV (Feingold & Rounsaville, 1995); the Brief Symptom Inventory (Derogatis, 1993); Brief Pain Inventory (BPI; Cleeland, 1989, 1990; Keller et al., 2004); Beck Depression Inventory (Beck et al, 1961); Beck Anxiety Inventory (Beck et al, 1988); Michigan Alcoholism Screening Test (Selzer, 1971); Fagerstrom Test of Nicotine Dependence (Heatherton et al., 1991); a Delay Discounting task (Kirby et al, 1999). We have used these instruments in prior studies (e.g., Dunn et al., 2008, 2010; Higgins, Sigmon et al., 2003; Sigmon et al., 2009, 2013, in prep).

At each visit, self-report of opioid and other drug use will be collected via Time-Line Followback (Sobell et al., 1988) and withdrawal and agonist effects assessed using the Clinical Institute Narcotic Assessment (Peachey & Lei, 1988). A modified version of the intake will be completed with all subjects at Weeks 4, 8, 12, 16, 20, 24, 36 and 48 post-randomization. These follow-ups will also include a Patient Satisfaction Questionnaire (Fiellin et al., 2001, 2006) and a brief assessment of overall interest, clarity and perceived effectiveness of IBT (and its individual components) on a Likert-type scale from 1 to 7. We will also collect qualitative data on (a) what aspects of the therapy patients liked and which ones they disliked, (b) patient suggestions to make the interventions better, (c) the extent to which participants utilized the IBT components. Participants will receive $30 per assessment independent of urine results, which has permitted high levels of compliance in our prior studies with illicit drug abusers (Higgins, Sigmon et al., 2003; Sigmon et al., 2009, 2013).

Interim Buprenorphine Treatment (IBT, n=35). Participants assigned to the IBT condition will complete an initial BUP stabilization week followed by IBT for 11 additional weeks. Participants will visit the clinic daily during Week 1 for induction onto an appropriate BUP dose. Thereafter, they will visit the clinic once every 1-2 weeks to ingest their BUP dose, provide a urine specimen and receive their remaining doses in the Med-O-Wheel. Additional details about the treatment components are provided below:

(1) Buprenorphine. IBT participants will receive buprenorphine sublingual tablets (Amneal Pharmaceuticals). Medication will be ordered and managed through our hospital's investigational pharmacy, which has prepared medications for our prior NIDA grants (e.g., Sigmon et al., 2009, 2013). BUP induction will occur in Week 1 (or longer if required), during which participants will attend the clinic daily. Self-report and observer ratings of withdrawal and agonist effects will be completed at each visit, and urine and breath samples will be collected to ensure no recent use of drugs contraindicated with BUP. Individualized induction will be conducted using a protocolized approach (Johnson et al., 2003; Sigmon et al., 2009, 2013). During Weeks 2-12, participants will visit the clinic once every two weeks to ingest their dose, provide a urine specimen and receive their remaining 13 doses dispensed in the Med-O-Wheel for ingestion at home. They can also return to the clinic between scheduled visits if any concerns arise or if a dose evaluation is needed.

(2) Computerized adherence monitoring. At each visit during Weeks 2-12, participants will receive their next 13 doses in the Med-O-Wheel device (Addoz, Forssa, Finland). Each day's dose will be secured in separate individually-locked compartments and the device will permit access during a 3-hour time window each day. Participants will be instructed to bring the device with them to each study visit, as well as random call-backs (below). They will be advised at intake and during Week 1 that any evidence of inappropriate CAM device use or suspicion of tampering with doses will be grounds for discharge from the study. Any participant failing to present the device on the first offense will be given a one-time opportunity to return within 12 hours with the intact Med-O-Wheel. Failure to do so, or a second offense, will result in termination of participation.

(3) *m*Health clinical support platform. IBT participants will receive basic support and monitoring via an IVR platform. The phone-based system will include branching logic that provides follow-up questions, messages and information in a seamless fashion, as well as immediate connection with a staff person or crisis service if needed (Rose et al., 2010). It will contact them each evening at a pre-determined time to assess any use of opioids or other drugs as well as any craving or withdrawal symptoms. It will follow up on reports of use, craving or withdrawal with additional detailed questions. Participants will also have the ability to make inbound

calls to the system to access clinical support at any time or to complete their daily check-in if they anticipate missing the call.

(4) Urinalysis and adherence monitoring. Random call-backs will occur approximately twice per month, during which participants will be contacted automatically via IVR and instructed to return to the clinic within approximately 12 hours. At each call-back, participants will provide a staff-observed urine specimen which will be analyzed immediately via enzyme multiplied immunoassay (Microgenics, Fremont, CA) for opioids (e.g., methadone, BUP, oxycodone, hydrocodone, heroin) and other drugs (e.g., cocaine, amphetamines, benzodiazepines, marijuana, barbiturates, cotinine). Breath alcohol samples will also be analyzed at the time of UA testing (ALCO-SENSOR III, Intoximeters, Inc., St. Louis, MO). Participants will also present their CAM device for inspection by staff to further ensure there is no evidence of tampering, nonadherence or diversion.

(5) HIV+Hepatitis education. Using an interactive iPad application, patients will complete a baseline assessment of HIV/hepatitis knowledge and perceived risk, after which the application will provide immediate corrective feedback of any incorrect items and include an explanation of the correct answer and its rationale. The patient will then watch an educational video that presents information on both drug- and sex-related HIV-risk behaviors, as well as information on hepatitis B and C. A second assessment will then be conducted, after which the application will again provide immediate feedback on all incorrect answers. At the end of the session, staff will offer condoms, information on HIV/hepatitis testing and other supplies if the participant desires. If a participant expresses interest in being tested, staff will provide them with the names of one or more facilities and their addresses, telephone numbers, and hours of operation.

Waitlist control (WLC, n=35). Participants assigned to the WLC will remain on the waiting list for their treatment of choice. They will visit the clinic to complete follow-up assessments and provide staff-observed urines according to the same schedule as IBT participants (Weeks 4, 8, 12, 16, 20, 24, 36, 48). WLC participants who have not entered agonist treatment by Week 12 (which we anticipate to be the majority) will be offered the opportunity to receive IBT for an additional 12-week period as described above. This will permit an additional within-subject opportunity to qualitatively evaluate the size of IBT effects, as well as being an ethical strength by providing WLC participants the opportunity to receive active treatment.

Statistical Methods

Pilot testing findings will be summarized by descriptive statistics of illicit opioid abstinence, treatment component utilization, quantitative rating scales and qualitative summaries of comments and suggestions. For the RCT, IBT and WLC groups will be compared on baseline characteristics using analyses of variance for continuous and chi-square tests for categorical variables. If characteristics differ significantly and are predictive of outcome, they will be considered as potential covariates in subsequent analyses. Primary analyses will include all randomized subjects independent of early dropout, consistent with an intent-to-treat approach (Armitage, 1983). Repeated measures analyses for categorical data based on generalized estimating equations (SAS, PROC GENMOD) will be used to compare IBT and WLC on percentage of subjects abstinent for illicit opioids across Week 4, 8, and 12 assessments. Chi square tests will be used to compare abstinence at each time point. Analyses of variance (SAS, PROC MIXED) will be used to compare groups on continuous outcomes (e.g., illicit opioid use, ASI subscale scores). We hypothesize that IBT participants will demonstrate greater reductions in illicit opioid use and criminal behavior than WLC participants. Additional repeated measures analyses will be performed within the IBT group that include the follow-up assessments to examine temporal patterns associated with abstinence during- and post-treatment. For WLC participants that cross over to IBT at Week 12, treatment condition will be represented by a within-subject factor in the generalized linear model. We hypothesize that illicit opioid use and criminal behavior will be significantly lower during their IBT vs. waitlist phase. Additional qualitative analyses will be used to characterize IBT-specific outcomes, including feasibility, acceptability, BUP adherence and retention. Analyses will be performed using SAS statistical software, V9.3 (SAS Institute, Cary, NC).

Sample Size Justification

Statistical significance will be determined based on α=.05 for all analyses. The proposed sample of 70 subjects is based on having sufficient power for detecting a group difference on the percent of participants negative for illicit opioids at Week 12. Power is estimated to be 90% using α=.05 if the true abstinence rates are 60% vs. 20% for the IBT and WLC groups, respectively. These estimates are based on the IMT study by Schwartz et al. (2006), with slightly higher abstinence expected in our IBT condition as it is more intensive than the intervention used in that trial.

HUMAN SUBJECTS RESEARCH

Protection of Human Subjects

The proposed study will be conducted at a single site, the Substance Abuse Treatment Center at the University of Vermont. The study will take place after complete review and approval by the local Institutional Review Board (IRB), the UVM Office of the Committee for Human Research in the Medical Sciences (CHRMS).

1. Risks to the Subjects

a. Human Subjects Involvement and Characteristics. Participants will be males and females who are currently awaiting methadone or buprenorphine maintenance treatment for opioid dependence. Participants must be ≥18 years old, in good health, meet DSM-IV criteria for opioid dependence, provide an opioid-positive urine at intake, and be currently waitlisted. To minimize the chance that participation will be disrupted due to a treatment slot becoming available during the 12-week study, we will limit enrollment to those who joined the waitlist in the prior 12 months. As noted earlier, 349 of the current CC census had joined the waitlist in the past 12 months (approximately 29 per month); thus, we do not expect this criterion to impede recruitment of the proposed 85 participants for this study. Those with a significant psychiatric (e.g., psychosis, manic-depressive illness, organic psychiatric disorders) or medical (e.g., cardiovascular disease) illness that may interfere with consent or participation will be excluded, as will those who are pregnant or nursing. Females will be tested for pregnancy prior to and during the study. Should a participant become pregnant during the trial, her participation will be terminated and she will be assisted with accessing treatment at the medical center's high-risk pregnancy clinic. Those dependent on sedative-hypnotics will also be excluded, due to the medical risks and notably low success rates with sedative-dependent opioid abusers (Stitzer & Chutuape, 1999). Participants must provide written informed consent to participate. Those meeting the above criteria and interested in an IBT study will be eligible for participation. Subjects are not a "vulnerable population" as defined by human subject's protection guidelines; that is, they are not pregnant women, under legal coercion or restriction, or mentally impaired. They are competent adults who provide their voluntary informed consent.

Study procedures will be conducted at UVM Buprenorphine Research Clinic, which has been the site of BUP research for the past 25 years. The clinic is located in our University Medical Center's outpatient building and is contiguous with our other research clinics for cocaine dependence and smoking cessation as well as our methadone clinic for which Dr. Sigmon is Director. Fifteen participants will take part in an initial pilot study. Participants in the randomized trial will be 70 opioid-dependent individuals. Study involvement will include participation in a 12-week randomized controlled trial in which 70 opioid-dependent adults wait-listed for agonist maintenance are randomized to receive IBT (n=35) or continue in a Waitlist Control condition (WLC; n=35). IBT participants will visit the clinic every 2 weeks while receiving the IBT package described above. WLC participants will remain on the waitlist for their treatment of choice, though they will complete the same scheduled follow-up assessments as IBT participants. WLC participants who have not entered treatment by Week 12 will be offered the opportunity to cross over to IBT at that time, contributing additional within-subject data with which to evaluate the efficacy of the IBT intervention.

b. Sources of Materials. Research materials will include questionnaires, structured clinical interviews, expired air samples for analyzing breath alcohol levels, urine samples for analyzing recent drug use and pregnancy status. All data will be collected for research purposes only. All data collection will be conducted by a trained bachelor's-level Research Assistant (RA) with special training on all forms and procedures. All information will be reviewed by the PI, who will determine participant eligibility and complete informed consent with eligible and willing participants. Subject data will be maintained in secure filing cabinets behind locked doors in order to protect confidential subject information. Safe places will include locked filing cabinets or locked rooms that will be accessible only to study personnel. Full subject names will not be listed on the outside of the binders in order to protect the identity of study participants. Subject data and subject identifiers will only be accessible to approved research staff.

c. Description of Potential Risks. Risks include breach of confidentiality and any side effects associated with the study medication (i.e., buprenorphine).

Breach of confidentiality. Study data include medical and psychiatric histories and biological measures of alcohol and illicit drug use and pregnancy. The likelihood of a breach of confidentiality is low as we will take precautions to minimize this risk as described below under Adequacy of Protection against Risk.

Side effects of buprenorphine. The side effects of buprenorphine include light-headedness, dizziness, sedation, lethargy, changes in sexual ability, nausea, vomiting, sweating, euphoria, constipation, respiratory depression, flushing of the face, skin itchiness or redness, darkening of the skin and/or swelling, bradycardia, headache, yawning, tearing, runny nose, muscle tremor, dilated or constricted pupil, restlessness, diarrhea, hypertension, hypotension, or potentially elevated liver enzyme levels (particularly among subjects with a history of hepatitis). The administration of the partial opioid agonist, buprenorphine, in individuals physically dependent on opioids should not result in acute toxicity because these individuals are tolerant to such drug

effects. There also is a ceiling on the agonist effects of partial agonists; thus, the agonist effects of the partial agonist, buprenorphine, are considered to be safer than full agonists. Because buprenorphine is a partial agonist, it could also function as an antagonist and promote withdrawal symptomatology. We will administer buprenorphine in accordance with standard practice (see Methods) and, based on our previous experience in treating opioid-dependent individuals with this medication (Sigmon et al., 2009; Sigmon et al., 2013, *JAMA Psychiatry*), we do not anticipate that buprenorphine-precipitated withdrawal or sedation will pose a problem.

2. Adequacy of Protection Against Risks

a. Recruitment and Informed Consent. The primary referral source will be distribution of an IRB-approved flyer to all CC waitlist individuals informing them about the study. Should this recruitment method ever become insufficient, we can also circulate ads throughout the larger community in order to reach additional patients on wait lists for BUP maintenance via OBOT. Additional sources will include self-referrals, drug abuse clinics, the Vermont State Alcohol and Drug Abuse Office, physicians, local mental health centers, a toll-free number, public service announcements, advertisements in local and alternative newspapers and flyers placed throughout the community. We have successfully recruited participants using these sources in prior studies (Dunn et al., 2008, 2010; Sigmon et al., 2009, in prep, 2013) and anticipate no difficulties gaining ready access to the sample needed.

Contact between participants and study staff will be initiated by the participants. Potential participants will respond to mailings or advertisements that contain a study description and the name and phone number of the Research Assistant. When potential participants call the Research Assistant, s/he will briefly describe the study and use a brief phone screen to make a preliminary determination about the potential participant's eligibility. Those who are interested in participating and appear to be eligible will be schedule for a longer intake screening that will begin with a full study description of study procedures. Those interested in undergoing study screening will then be provided with a copy of the consent form to read as we go over it with them. Risks and benefits of the study will be described. Potential participants will be asked to paraphrase the consent form and will be asked questions to determine their understanding of key elements of the informed consent. Potential participants who wish to proceed with the interview will be asked to sign the interview consent form and will be given a signed copy of his/her signed consent form.

b. Protection Against Risk. (1) To protect confidentiality, the guidelines stated in Title 42 of the Code of Federal Regulations, Part 2, "Confidentiality of Alcohol and Drug Abuse Records" will be followed. As stated in these regulations, subjects will be given a notice of federal confidentiality requirements (which will be included in the consent form). All records will be locked in file cabinets kept on site behind locked doors. Except for intake material, subjects' names (i.e., first and last names) will not be attached to the data forms. A central code/data base linking subject number with subject names will be kept, which will be available only to specified staff.

(2) In order to protect participants from any adverse effects of buprenorphine, a number of safeguards will be in place. First and most generally, subjects will be screened thoroughly at intake using medical, psychiatric, drug abuse, and cognitive interviews and self-reports. They will have a complete physical exam, and follow-up interviews and tests may be ordered to clarify results. The results of all tests will be reviewed by the medical director (Dr. Brooklyn) and the PI (Dr. Sigmon). Thus, we will document that the patient is healthy to participate in the proposed study. To prevent subjects who may have an insufficient level of opioid dependence from participating in these studies, they will have to meet several criteria (e.g., DSM-IV criteria for opioid dependence and FDA qualification criteria for buprenorphine treatment, including a history of opioid dependence and significant current opioid use). All medication administration will occur during working hours at the University Health Center (UHC), an inpatient/outpatient facility of the University of Vermont College of Medicine and Fletcher Allen Health Care. Numerous physicians are on the same floor as the clinic. All nursing and research staff will be trained by medical staff in detecting adverse effects. If a subject has any untoward effects, the Study Physician and PI will be contacted. Study Physician Dr. Brooklyn will be on-call continuously for advice and assistance in the event that adverse effects occur. Dr. Brooklyn has been working with our previous buprenorphine projects over the last 15 years, is a buprenorphine provider, is Medical Director of the Chittenden Clinic methadone program, and he has extensive experience with the clinical use of buprenorphine as a Vermont buprenorphine provider and trainer. The emergency room for the Fletcher Allen Hospital of Vermont is located approximately one block away from the UHC.

(3) Finally, patients are free not to participate in this study or to withdraw from it at any time. If they decide not to participate in the study, we will be glad to discuss with them other treatments that may be available in Vermont, including residential, outpatient, and medication-assisted treatment options. If patients decide not to

participate in this study or to withdraw from this study, their decision will not prejudice their future medical care at the University of Vermont or Fletcher Allen Health Care. The investigators also retain the right to terminate patients' participation in the study if in their judgment continued participation would put them in physical or psychological danger. Additional details on our data and safety monitoring of the proposed research to ensure the safety of subjects is provided in the below section entitled "Data and Safety Monitoring Plan".

3. Potential Benefits to Participants and Others

Volunteers may benefit by initiating abstinence from illicit opioids during their study participation, including experiencing a reduction in the wide range of medical, financial, psychosocial, and legal consequences associated with illicit opioid abuse. Volunteers may also benefit from the financial compensation provided as part of the proposed study. By improving treatment access for opioid abuse and dependence, the proposed research also stands to benefit public health in general by reducing the vast economic and societal costs associated with opioid abuse (e.g., health service utilization and costs, criminal activity, contraction of preventable diseases such as HIV and hepatitis). In addition, there are potential scientific benefits to be gained by expanding our empirical knowledge on how to mitigate gaps in treatment access among opioid-dependent individuals. Overall, the individual participant, the medical and scientific communities, and society in general may benefit by our efforts to develop an interim buprenorphine treatment for patients awaiting agonist maintenance. As such, the risks to which individuals may be exposed as a function of their research participation are reasonable in relation to the anticipated benefits.

4. Importance of the Knowledge to be Gained

The proposed project has the potential to contribute a novel and effective technology-assisted pharmacotherapy protocol that can be widely disseminated to bridge gaps in access to life-saving opioid treatment. Thus, knowledge gained from this research may significantly enhance the accessibility, implementation and effectiveness of drug abuse treatment more generally. Consequently, the risk/benefit ratio is favorable. The risks to which individuals are exposed as a consequence of their research participation are generally less than that associated with continuing their ongoing abuse of illicit opioids. In contrast, the potential and probable benefits to be derived by society in general and by opioid abusers as a group are considerable. In summary, conducting this research seems well justified.

DATA AND SAFETY MONITORING PLAN

The proposed study presents low risk to participants. Our overall monitoring plan consists of continuous, close monitoring by the PI and Co-Investigators, as well as prompt reporting of any adverse events (AEs) or serious adverse events (SAEs) to the UVM IRB/CHRMS and/or NIH, as suggested by Notice OD-00-038. We provide more detail below regarding particular areas recommended by PA-03-066 and Notice OD-00-038.

Patient eligibility and status. All intake data collection will be conducted by a trained bachelor's-level Research Assistant (RA) using specialized forms and procedures. Medical screening data will be reviewed by the Study Physician. All intake information will be reviewed by the PI, who will determine participant eligibility. Only trained and IRB-approved research staff will complete informed consent with eligible and willing participants. The status of all active participants will be reviewed at weekly meetings between the PI, Co-investigators and RAs.

Rigorous data management/Quality assurance. The majority of study data collection will be conducted using self-report questionnaires. Randomly selected data will be checked by the RAs for completeness and to ensure quality (i.e., no appearance of rote answers, etc.). In terms of standard operating procedures at the clinic, all assessments will be administered by trained research staff. All subject data will be maintained in secure filing cabinets behind locked doors in order to protect confidential subject information. Safe places will include locked filing cabinets or locked rooms that will be accessible only to study personnel. Full subject names will not be listed on the outside of the binders in order to protect the identity of study participants. Moreover, all data that are entered into spreadsheets and databases, in preparation for data analyses, will be entered twice. That is, two separate individuals will enter the data into databases, and a comparison between data entries will be conducted to detect data entry errors. All discrepancies in data entry will be checked against the raw data source, and the correct data entry will be used. All data that are entered into spreadsheets and databases will be coded by subject ID number and not by subject name. Additionally, all entered data will be backed up on an external hard drive or a secure project server at least weekly. The biostatistician and PI will discuss any problems at monthly data meetings. Additional meetings will be

conducted on an as-needed basis. An original copy of the data will be retained at the clinic should anything happen to the document during transmission.

Auditing procedures. Review of any problems related to quality of data collection, transmission or analyses and of any AEs and SAEs that occurred during the past week will occur at weekly research staff meetings. Interim analyses of efficacy data will be conducted when half the subjects have been entered or at other times based on the joint discretion of the PI, Co-I and biostatistician.

Reporting mechanisms of AEs & SAEs to the CHRMS and NIDA. In the proposed study, we will use the FDA's definition of AEs and SAEs. AEs and SAEs will be assessed at each clinic visit by a trained RA and copies of all reports noting AEs and SAEs will be kept in a central file as well as in the individual subject's chart. AEs will be discussed at the weekly research staff meetings. Any SAE will be brought to the attention of the PI as soon as possible and not longer than 24 hrs. The NIDA project officer will be notified of SAEs within 72 hrs. Any SAE, whether or not related to study intervention, will be reported to the IRB's CHRMS using the University of Vermont Adverse Event Reporting Document within 5 days of the event. Copies of these reports will be forwarded to the NIDA Project Officer at the same time that they are sent to the CHRMS. This will be the responsibility of the PI. The CHRMS will make a determination as to whether additional reporting requirements are needed. CHRMS actions will be reported to NIDA by the PI no less than annually and more frequently as recommended by the local CHRMS. Any SAEs will be summarized in the yearly NIDA Progress Report, including a review of frequency and severity. All SAEs will be followed through ongoing consultation with the physician caring for the patient until they resolve, result in death, or stabilize and are not expected to improve.

Data Sharing Plan. After all data have been collected and the results of the study have been published, de-identified data will be made available to other qualified investigators upon request. The request will be evaluated by the PI and Co-Investigators to ensure that it meets reasonable demands of scientific integrity.

LITERATURE CITED

Abbott, P.J., Moore, B.A., Delaney, H.D., & Weller, S. (1999). Retrospective analyses of additional services for methadone maintenance patients. *J Subst Abuse Treat, 17*,129-137.

Abbott, P.J., Weller, S.B., Delaney, H.D., & Moore, B.A. (1998). Community reinforcement approach and relapse prevention in the treatment of opioid dependency. *Am J Drug Alcohol Abuse, 24*, 17-30.

Adamson, S. J., & Sellman, D. (1998). The pattern of intravenous drug use and associated criminal activity in patients on a methadone treatment waiting list. *Drug Alcohol Rev, 17*, 59−166.

Amass, L., Bickel, W.K., Crean, J.P., Blake, J., & Higgins, S.T. (1998). Alternate-day buprenorphine dosing is preferred to daily dosing in opioid-dependent humans. *Psychopharmacol, 136*, 217-225.

Amass, L., Bickel, W.K., Higgins, S.T., & Badger, G.J. (1994a). Alternative-day dosing during buprenorphine treatment of opioid dependence. *Life Sciences, 54*, 1215-1228.

Amass, L., Bickel, W.K., Higgins, S.T., & Hughes, J.R. (1994b). A preliminary investigation of outcome following gradual or rapid buprenorphine detoxification. *J Addict Dis, 13*, 33-45.

Arnsten, J.H., Demas, P.A., Farzadegan, H., Grant, R.W., Gourevitch, M.N., et al. (2001). Antiretroviral therapy adherence and viral suppression in HIV-infected drug users: Comparison of self-report and electronic monitoring. *Clin Infect Dis, 33*(8), 1417-1423.

Badiee, J., Riggs, P.K., Rooney, A.S., Vaida, F., Grant, I., et al. (2012). Approaches to identifying appropriate medication adherence assessments for HIV infected individuals with comorbid bipolar disorder. *AIDS Patient Care STDS, 26*(7), 388-394.

Ball, J.C., & Ross, A. (1991). *The effectiveness of methadone maintenance treatment*. New York: Springer-Verlag.

Banks, C.D. (1979). Overdosage of buprenorphine: case report. *NZ Med. J. 89*, 255–256.

Barry, D.T., Irwin, K.S., Jones, E.S., Becker, W.C., Tetrault, J.M., et. al. (2008). Integrating buprenorphine treatment into office-based practice: A qualitative study. *J Gen Intern Med, 24*(2), 218-225.

Beck, A.T., Epstein, N., Brown, G., & Steer, R.A. (1988). An inventory for measuring clinical anxiety: Psychometric properties. *J Consult Clin Psych, 56*, 893-897.

Beck, A.T., Ward, C.H., Mendelson, M., Mock, J., & Erbaugh, J. (1961). An inventory for measuring depression. *Arch Gen Psychiat, 4*, 561-571.

Becker, W. C., & Fiellin, D. A. (2006). Provider satisfaction with office- based treatment of opioid dependence a systematic review. *Subst Abuse, 26*, 15−22.

Becker, W.C., Sullivan, L.E., Tetrault, J.M., Desai, R.A., & Fiellin, D.A. (2008). Non-medical use, abuse and dependence on prescription opioids among U.S. adults: Psychiatric, medical and substance use correlates. *Drug Alc Depend, 94*, 38-47.

Beebe, K.L., Chavoustie, S., Ling, W., Sigmon, S., Leiderman, D.B., & Bailey, G. (2012). Buprenorphine implants for the treatment of opioid dependence: Six- and 12-month outcomes. Presented at the 51st annual meeting of the American College of Neuropsychopharmacology.

Bickel, W.K., Marsch, L.A., Buchhalter, A.R., & Badger, G.J. (2008). Computerized behavior therapy for opioid-dependent outpatients: a randomized controlled trial. *Exp Clin Psychopharmacol, 16*(2):132-43.

Bickel, W.K., & Amass, L. (1995). Buprenorphine treatment of opioid dependence: A review. *Exp Clin Psychopharmacol, 3*, 477-489.

Bickel, W.K., Amass, L., Higgins, S.T., Badger, G.J., & Esch, R.A. (1997). Effects of adding behavioral treatment to opioid detoxification with buprenorphine. *J Consult Clin Psych, 65*, 803-810.

Bickel, W.K., Stitzer, M.L., Bigelow, G.E., Liebson, I.A., Jasinski, D.R., et al. (1998). Buprenorphine: dose-related blockade of opioid challenge effects in opioid dependent humans. *J Pharmacol Exp Ther, 247*, 47–53.

Birnbaum, H.G., White, A.G., Schiller, M., Waldman, T., Cleveland, J.M. et al. (2011). Societal costs of prescription opioid abuse, dependence and misuse in the United States. *Pain Med, 12*(4), 657-667.

Boyer, E.W., Smelson, D., Fletcher, R., Ziedonis, D., & Picard, R.W. (2010). Wireless technologies, ubiquitous computing and mobile health: application to drug abuse treatment and compliance with HIV therapies. *J Med Toxicol, 6*, 212-216.

Centers for Disease Control and Prevention (CDC). (2008). Disease burden from Viral hepatitis A, B, and C in the United States. Division of Viral Hepatitis, National Center for HIV/AIDS, Viral Hepatitis, STD and TB Prevention. Accessed on 04/23/2013 at: http://www.cdc.gov/hepatitis/Statistics/index.htm

Centers for Disease Control and Prevention (CDC). (2011). HIV Surveillance Report: Diagnoses of HIV infection and AIDS in the United States and Dependent Areas, Vol. 23. Accessed on 04/23/2013 at: http://www.cdc.gov/hiv/topics/surveillance/basic.htm

Chermack, S. T., Roll, J., Reilly, M., Davis, L., Kilaru, U., et al. (2000). Comparison of patient self-reports and urinalysis results obtained under naturalistic methadone treatment conditions. *Drug Alcohol Depend, 59*(1), 43-49.

Clausen, T., Waal, H., Thoresen, M., & Gossop, M. (2009). Mortality among opiate users: Opioid maintenance therapy, age and causes of death. *Addiction, 104*, 1356-1362.

Cleeland, CS. (1989). Measurement of Pain by Subjective Report. Iss Pain Meas. Vol. 12. New York: Raven Press, pp 391–403.

Cleeland, C.S. (1990). Assessment of Pain in Cancer: Measurement Issues. *Proceedings of the Second International Congress on Cancer Pain*. Vol. 16. New York: Raven Press, pp 47–56.

Cone, E.J. & Dickerson, S.L. (1992). Efficacy of urinalysis in monitoring heroin and cocaine abuse patterns: Implications in clinical trials for treatment of drug dependence. *NIDA Res Monogr, 128*, 46-58.

Cooper, J. R. (1989). Methadone treatment and acquired immunodeficiency syndrome. *JAMA, 262*,1664–1668.

Copenhaver, M.M., Johnson, B.T., Lee, I.C., Harman, J.J., Carey, M.P., & SHARP Research Team. (2006). Behavioral HIV risk reduction among people who inject drugs: Meta-analytic evidence of efficacy. *J Subst Abuse Treat, 31*(2), 163-171.

Correia, C.J., Sigmon, S.C., Silverman, K., Bigelow, G., & Stitzer, M.L. (2005). A comparison of voucher delivery schedules for the initiation of cocaine abstinence. *Exp Clin Psychopharmacol, 13*, 253-258.

Crawford, A.G., Sikirica, V., Goldfarb, N., Popiel, R.G., Patel, M., et al. (2005). Interactive voice response reminder effects on preventive service utilization. *Am J Med Qual, 20*(6), 329-336.

Darke, S., & Hall, W. (2003). Heroin overdose: Research and evidence-based intervention. *J Urban Health, 80*, 189–200.

Department of Vermont Health Access (2012). Vermont hub and spoke health homes: Program and payment overview. State of Vermont Department of Health, http://dvha.vermont.gov/administration/1hub-spoke-health-home-framework-payment-12-10-12.pdf

Derogatis, L.R. (1993). Brief Symptom inventory. Minneapolis, MN: National Computer Systems, Inc.

Des Jarlais, D.C., Paone, D., Friedman, S.R., Peyser, N., & Newman, R.G. (1995). Regulating controversial programs for unpopular programs for unpopular people: Methadone maintenance and syringe exchange programs. *Am J Public Health, 85*, 1577−1584.

Donovan, D.M., Rosengren, D.B., Downey, L., Cox, G.B., & Sloan, K.L. (2001). Attrition prevention with individuals awaiting publicly funded drug treatment. *Addiction 96* (8), 1149–60.

Dunn, K., Sigmon, S.C., Saulsgiver, K., Patrick, M., Heil, S.H., et al. (in preparation). Characterizing opioid withdrawal severity and timecourse during double-blind, outpatient buprenorphine detoxification.

Dunn, K.E., Saulsgiver, K.A., Patrick, M.E., Heil, S.H., Higgins, S.T., & Sigmon, S.C. (2013). Characterizing and improving HIV and hepatitis knowledge among primary prescription opioid abusers. Drug and Alcohol Dependence, 133, 625-632.Dunn, K.E., Sigmon, S.C., Heil, S., & Higgins, S.T. (June 2008a). *Semi-quantitative buprenorphine testing in an ongoing study with prescription opioid abusers.* Poster presentation at the 70th Annual Meeting of the College on Problems of Drug Dependence, San Juan, PR.

Dunn, K.E., Sigmon, S.C., McGee, M.R., Heil, S.H., & Higgins, S.T. (2008b). Evaluation of ongoing oxycodone abuse among methadone-maintained patients. *J Subst Abuse Treat, 35*, 451-456.

Dunn, K.E., Sigmon, S.C., Reimann, E., Heil, S.H., & Higgins, S.T. (2009). Effects of smoking cessation on illicit drug use among opioid maintenance patients. *J Drug Issues, 39*(2), 313-328.

Dunn, K.E., Sigmon, S.C., Reimann, E.F., Badger, G.J., Heil, S.H., et al. (2010). A contingency-management intervention to promote initial smoking cessation among opioid-maintained patients. *Exp Clin Psychopharmacol, 18* (1), 37-50.

Dunn, K.E., Sigmon, S.C., Strain, E., Heil, S.H., & Higgins, S.T. (2011a). The association between outpatient buprenorphine detoxification duration and clinical treatment outcomes: A review. *Drug Alcohol Depend, 119* (1-2), 1-9.

Dunn, K.E., Sigmon, S.C., Thomas, C.S., Heil, S.H., & Higgins, S.T. (2008c). Voucher-based contingent reinforcement of smoking abstinence among methadone-maintained patients: A pilot study. *J Appl Behav Anal, 41*, 527-538.

Edelman, E.J., Dinh, A., Moore, B.A., Schottenfeld, R.S., Fiellin, D.A., et al. (2012). HIV testing practices among buprenorphine-prescribing physicians. *J Addict Med, 6;*159-165.

European Monitoring Centre for Drugs and Drug Addiction. (2010). *Annual report 2010: the state of the drugs problem in Europe.* Luxembourg: Publications Office of the European Union
http://www.emcdda.europa.eu/attachements.cfm/att_120104_EN_EMCDDA_AR2010_EN.pdf

Fazzino, T.L., Harder, V.S., Rose, G.L., & Helzer J.E. (in press). A daily process examination of the bidirectional relationship between craving and alcohol consumption as measured via Interactive Voice Response (IVR). Alcohol Clin Exp Res.

Feingold, A., & Rounsaville, B. (1995). Construct validity of the dependence syndrome as measured by DSM-IV for different psychoactive substances. *Addiction, 90*, 1661-1669.

Fendrich, M., Johnson, T. P., Wislar, J. S., Hubbell, A., & Spiehler, V. (2004). The utility of drug testing in epidemiological research: Results from a general population survey. *Addiction, 99*(2), 197-208.

Festinger, D.S., Lamb, R.J., Kountz, M.R., Kirby, K.C., & Marlowe, D. (1995). Pretreatment dropout as a function of treatment delay and client variables. *Addict Behav, 20*(1),111–5.

Fiellin, D.A., Moore, B.A., Sullivan, L.E., Becker, W.C., Pantalon, M.J., et al. (2008). Long-term treatment with buprenorphine/noloxone in primary care: Results at 2-5 year follow-up. *Am J Addict, 17*, 116-120.

Fiellin, D.A., O'Connor, P.G., Chawarski, M., Pakes, J.P., Pantalon, M.V. et al. (2001). Methadone maintenance in primary care: A randomized controlled trial. *JAMA, 286*(14), 1724-1731.

Fiellin, D.A., Pantalon, M.V., Chawarski, M.C., Moore, B.A., Sullivan, L.E., et al. (2006). Buprenorphine maintenance in primary care: A randomized controlled trial of counseling conditions and medication dispensing. *NEJM, 355*(4), 365-374.

Fortney, J. & Booth, B.M. (2001). Access to substance abuse services in rural areas. *Recent Dev Alcohol, 15*:177-197.

Fountain, J., Strang, J., Griffiths, P., Powis, B., & Gossop, M. (2000). Measuring met and unmet need of drug misusers: Integration of quantitative and qualitative data. *European Addiction Research, 6*, 97−103.

French, M.T., McCollister, K.E., Cacciola, J., Durell, J., & Stephens, R.L. (2002a). Benefit-cost analysis of addiction treatment in Arkansas: specialty and standard residential programs for pregnant and parenting women. *Substance Abuse, 23*, 31-51.

French, M.T., Salome, H.J., Sindelar, J.L., & McLellan, A.T. (2002b). Benefit-cost analysis of addiction treatment: methodological guidelines and empirical application using the DATCAP and ASI. *Health Serv Res, 37*, 433-455.

Friedmann, P.D., Lemon, S.C., Stein, M.D., & D'Aunno, T.A. (2003). Accessibility of addiction treatment: Results from a national survey of outpatient substance abuse treatment organizations. *Health Serv Res, 38*(3), 887-903.

Gallalee, S., Sigmon, S.C. & Cope, M. (in preparation). Access to treatment for opioid abuse: A geographic analysis of Vermont.

García-Fernández, G., Secades-Villa, R., García-Rodríguez, O., Alvarez-López, H., Fernández-Hermida, J.R., et al. (2011a). Long-term benefits of adding incentives to the community reinforcement approach for cocaine dependence. *Eur Addict Res, 17*(3), 139-45.

García-Fernández, G., Secades-Villa, R., García-Rodríguez, O., Sánchez-Hervás, E., et al. (2011b). Adding voucher-based incentives to community reinforcement approach improves outcomes during treatment for cocaine dependence*. Am J Addict, 20*(5), 456-61

García-Rodríguez, O., Secades-Villa, R., Higgins, S.T., Fernández-Hermida, J.R., & Carballo, J.L. (2008). Financing a voucher program for cocaine abusers through community donations in Spain. *J Appl Behav Anal, 41*(4), 623-8.

Garcia-Rodriguez, O., Secades-Villa, R., Higgins, S.T., Fernandez-Hermida, J.R., Carballo, J.L., et al. (2009). Effects of voucher-based intervention on abstinence and retention in an outpatient treatment for cocaine addiction: A randomized controlled trial. *Exp Clin Psychopharmacol, 17*(3), 131-8.

Greenwald, M.L., Johanson, C.-E., Moody, D.E. , Woods, J.H., Kilbourn, M.R., et al. (2003). Effects of buprenorphine maintenance dose on u-opioid receptor availability, plasma concentrations, and antagonist blockade in heroin-dependent volunteers. *Neuropsychopharmacology*, 28*,* 2000-2009.

Gruber, V. A., Delucchi, K. L., Kielstein, A., & Batki, S. L. (2008). A randomized trial of 6-month methadone maintenance with standard or minimal counseling versus 21-day methadone detoxification. *Drug Alcohol Depend, 94*, 199-206.

Gryczynski, J., Schwartz, R., O'Grady, K., & Jaffe, J. (2009). Treatment entry among individuals on a waiting list for methadone maintenance. *Am J Drug Alcohol Abuse, 35*(5), 290-294.

Harford, R.J., & Kleber, H.D. (1978). Comparative validity of random-interval and fixed-interval urinalysis schedules. *Arch Gen Psychiatry, 35*(3), 356-359.

Heatherton, T. F., Kozlowski, L. T., Frecker, R. C., & Fagerström, K. O. (1991). The Fagerström Test for Nicotine Dependence: a revision of the Fagerström Tolerance Questionnaire. *Br J Addict, 86*(9), 1119-27.

Heil, S.H., Gaalema, D.E., Johnston, A.M., Sigmon, S.C., Badger, G.J., et al. (2012). Infant pupillary response to methadone administration during treatment for neonatal abstinence syndrome: A feasibility study. *Drug Alcohol Depend, 126*(1-2), 268-271.

Heil, S.H., Sigmon, S.C., Jones, H.E., & Wagner, M. (2008). Comparison of characteristics of opioid-using pregnant women in rural and urban settings. *Am J Drug Alcohol Dep, 34*, 463-471.

Heil, S.H., Sigmon, S.C., Mongeon, J.A., & Higgins, S.T. (2005). Characterizing and improving HIV/AIDS knowledge among cocaine-dependent outpatients. *Exp Clin Psychopharmacol, 13*(3), 238-243.

Helzer, J.E., Rose, G.L., Badger, G.J., Searles, J.S.,Thomas, C.S., et al. (2008). Using Interactive Voice Response to Enhance Brief Alcohol Intervention in Primary Care Settings. *J Stud Alcohol Drugs, 69,* 251-258.

Helzer, J.E., Badger, G.J., Searles, J.S., Rose, G.L., & Mongeon, J.A. (2006). Stress and alcohol consumption in heavy drinking men: Two years of daily data using Interactive Voice Response (IVR). *Alcohol Clin Exp Res, 30*, 802-811.

Herrmann, E.S., Heil, S.H., Sigmon, S.C., Dunn, K.E., Washio, Y., & Higgins, S.T. (2013). Characterizing and improving HIV/AIDS knowledge among cocaine-dependent outpatients using modified materials. *Drug Alcohol Depend, 127*(1-3), 220-225.

Higgins, S.T., Badger, G.J., & Budney, A.J. (2000b). Initial abstinence and success in achieving longer-term cocaine abstinence. *Exp Clin Psychopharmacol, 8*, 377-386.

Higgins, S.T., Budney, A.J., & Bickel, W.K. (1994a). Applying behavioral concepts and principles to the treatment of cocaine dependence. *Drug Alcohol Depend, 34*(2), 87-97.

Higgins, S.T., Budney, A.J., Bickel, W.K., Foerg, F.E., Donham, R. et al. (1994b). Incentives improve outcome in outpatient behavioral treatment of cocaine dependence. *Arch Gen Psychiatry, 51*, 568-576.

Higgins, S.T., Budney, A.J., Bickel, W.K., Hughes, J.R., Foerg, F. et al. (1993). Achieving cocaine abstinence with a behavioral approach. Am J Psychiatry, 150, 763-769.

Higgins, S.T., Delaney, D.D., Budney, A.J., Bickel, W.K., Hughes, J.R. et al. (1991). A behavioral approach to achieving initial cocaine abstinence. *Am J Psychiatry, 148*, 1218-1224

Higgins, S.T., Sigmon, S.C., Wong, C.J., Heil, S.H., Badger, G.J. et al. (2003). Community reinforcement therapy for cocaine-dependent outpatients. *Arch Gen Psychiatry, 60*, 1043-1052. (PMID: 14557150)

Higgins, S.T., Silverman, K., Sigmon, S.C., & Naito, N.A. (2012a). Incentives and health: An introduction. *Prev Med, 55*, 2-6.

Higgins, S.T., Stitzer, M.L., Bigelow, G.E., & Liebson, I.A. (1986). Contingent methadone delivery: Effects on illicit opiate use. *Drug Alcohol Depend, 17*, 311-322.

Higgins, S.T., Stitzer, M.L., McCaul, M.E., Bigelow, G.E., & Liebson, I.A. (1985). Pupillary response to a methadone challenge in chronic heroin users. *Clin Pharmacol Ther, 37*, 460-463.

Higgins, S.T., Washio, Y., Heil, S.H., Solomon, L.J., Gaalema, D.E. et al. (2012b). Financial incentives for smoking cessation among pregnant and newly postpartum women. *Prev Med, 55*, 33-40.

Higgins, S.T., Heil, S.H., Dantona, R., Donham, R., Matthews, M. et al. (2007). Effects of varying the monetary value of voucher-based incentives on abstinence achieved during and following treatment among cocaine-dependent outpatients. *Addiction, 102*(2), 271-281.

Hser, Y.I., Hoffman, V., Grella, C.E. & Anglin, M.D. (2001). A 33-year follow-up of narcotic addicts. *Arch Gen Psychiatry, 58*(5):503-508.

Hser, Y.I., Maglione, M., Polinsky, M.L., & Anglin, M.D. (1998). Predicting drug treatment entry among treatment-seeking individuals. *J Subst Ab Treat, 15*(3), 213-220.

Institute of Medicine (IOM). (1995). In R. A. Retting, & A. Yarmolinsky (Eds.) Federal regulation of methadone treatment. Washington, DC: National Academy Press.

Jasinski, D.R., Pevnick, J.S., & Griffith, J.D. (1978). Human pharmacology and abuse potential of the analgesic buprenorphine. *Arch. Gen. Psychiatry 35*, 501–516.

Johanson, C.E., Arfken, C.L., di Menza, S., & Schuster, C.R. (2012). Diversion and abuse of buprenorphine: Findings from national surveys of treatment patients and physicians. 120(1-3):190-195.

Johnson, R.E., Chutaupe, M.A., Strain, E.C., Walsh, S.L., Stitzer, M.L. et al.(2000). A comparison of levomethadyl acetate, buprenorphine, and methadone for opioid dependence. *N Engl J Med, 343*(18):1290-1297.

Johnson, R.E., Strain, E.C., & Amass, L. (2003). Buprenorphine: How to use it right. *Drug Alcohol Depend, 70*, S59-S77.

Jones, H.E., Kaltenbach, K., Heil, S.H., Stine, S.M., Coyle, M.G. et al. (2010). Neonatal abstinence syndrome following methadone or buprenorphine exposure. *N Engl J Med, 363*, 2320-2331.

Kaplan, E. H., & Johri, M. (2000). Treatment on Demand: An Operational Model. *Health Care Manag Sci, 3*(3): 171–83.
Keller, S., Bann, C.M., Dodd, S.L., Schein, J., Mendoza, T.R., et al. (2004). Validity of the Brief Pain Inventory for use in documenting the outcomes of patients with noncancer pain. *Clin J Pain, 20*, 309-318.
Kilpatrick, B., Howlett, M., Sedgwick, P., & Ghodse, A. H. (2000). Drug use, self report and urinalysis. *Drug Alcohol Depend, 58*(1-2), 111-116.
Kim, H., Bracha, Y., & Tipnis, A. (2007). Automated depression screening in disadvantaged pregnant women in an urban obstetric clinic. *Arch Womens Ment Health, 10*(4), 163-169.
Kirby, K.N., Petry, N.M., & Bickel, W.K. (1999). Heroin addicts have higher discount rates for delayed rewards than non-drug-using controls. *J Exp Psychol Gen, 128*(1), 78-87.
Kissin, W., McLeod, C., et al. (2006). Experiences of a national sample of qualified addiction specialists who have and have not prescribed buprenorphine for opioid dependence. *J Addict Dis, 25*, 91−103
Larney, S., Randall, D., Gibson, A., & Degenhardt, L. (2012). The contributions of viral hepatitis and alcohol to liver-related deaths in opioid-dependent people. *Drug and Alcohol Dependence*, (epub ahead of print)
Lenardson, J., Gale, J.A. (2007). Distribution of substance abuse treatment facilities across the rural-urban continuum. U.S. Department of Health and Human Services, Federal Office of Rural Health Policy. Portland, ME. http://muskie.usm.maine.edu/Publications/rural/wp35b.pdf.
Lewis, J.W. (1985). Buprenorphine. Drug Alcohol Dep, 14, 363-372.
Luty, J., O'Gara, C., & Sessay, M. (2005). Is methadone too dangerous for opiate addiction? BMJ, 331(7529), 1352-1353.
Manno, J.E. (1986). Specimen collection and handling. NIDA Res Monogr, 73, 24-29.
McClure, E.A., Acquavita, S.P., Harding, E., & Stitzer, M.L. (2013). Utilization of communication technology by patients enrolled in substance abuse treatment. *Drug Alcohol Depend, 129*, 145-150.
McLellan, A. T., Arndt, I. O., Metzger, D. S., Woody, G. E., & O'Brien, C. P. (1993). The effects of psychosocial services in substance abuse treatment. *JAMA, 269*, 1953-1959.
McLellan, A.T., Luborsky, L., & Cacciola, J. (1985). New data from the Addiction Severity Index: Reliability and validity in three centers. *J Nerv Ment Dis, 173*, 412-423.
Meader, N. (2010). A comparison of methadone, buprenorphine and alpha(2) adrenergic agonists for opioid detoxification: A mixed treatment comparison meta-analysis. *Drug Alcohol Depend, 108*(1-2), 110-114.
Mello, N.K. & Mendelson, J.H. (1980). Buprenorphine suppresses heroin use by heroin addicts. *Science, 207*, 657–659.
Mello, N.K., Mendelson, J.H. & Kuehnle, J.C. (1982). Buprenorphine effects on heroin self-administration: an operant analysis. *J Pharmacol Exp Ther, 223*, 30–39.
Moore, B.A., Barry, D.T., Cutter, C.J., Sullivan, L.E., O'Connor, P.G., et al. (2012). Counseling and directly observed medication for primary care buprenorphine/naloxone maintenance: A pilot study. *J Addict Med, 6*:205-211.
Moore, B.A., Fazzino, T., Garnet, B., Cutter, C., & Barry, D. (2011). Computer-based interventions for drug use disorders: A systematic review. *J Subst Abuse Treat*, 40:215-223.
Moore, B.A., Fiellin, D.A., Barry, D.T., Sullivan, L.E., Chawarski, M., et al. (2007). Primary care office-based buprenorphine treatment: Comparison of heroin and prescription-opioid dependent patients. *J Gen Intern Med, 22,* 527-530.
Moore, B.A., Fazzino, T., Barry, D.T., Fiellin, D.A., Cutter, C.J., et al. (2013). The Recovery Line: A pilot trial of automated, telephone-based treatment for continued drug use in methadone maintenance. *J Subst Abuse Treat, 45*, 63-69.
Netherland, J., Botsko, M., Egan, J.E., Saxon, A.J., Cunningham, C.O., et al. (2009). Factors affecting willingness to provide buprenorphine treatment. *J Subst Abuse Treat*, 36, 244-251.
Office of National Drug Control Policy (ONDCP). (2008). Vermont drug control update. http://www.whitehouse.gov/sites/default/files/docs/state_profile_-_vermont.pdf.
Peachey, J. E. & Lei, H. (1988). Assessment of opioid dependence with naloxone. *Br J Addict, 83*(2), 193-201.
Peles, E., Schreiber, S., & Adelson, M. (2013). Opiate-dependent patients on a waiting list for methadone maintenance treatment are at high risk for mortality until treatment entry. *J Addict Med,* doi: 10.1097/ADM.0b013e318287cfc9
Peles, E., Schreiber, S., Sason, A., & Adelson, M. (2012). Long waiting period to enter methadone maintenance treatment: Relation to patient characteristics and outcome. *Eur Addict Res, 18*(3), 149-152.

Peterson, J.A., Schwartz, R.P., Mitchell, S.G., Reisinger, H.S., Kelly, S.M., et al. (2010). Why don't out-of-treatment individuals enter methadone treatment programmes? *Int J Drug Policy, 21,* 36-42.

Preston, K.L., Silverman, K., Schuster, C.R., Cone, E.J. (1997). Comparison of self-reported drug use with quantitative and qualitative urinalysis for assessment of drug use in treatment studies. *NIDA Res Monogr*, 167:130-45.

Rosado, J., Sigmon, S.C., Jones, H., Chilsolm, C., & Stitzer, M.L. (2005). Cash value of voucher reinforcers in pregnant drug-dependent women. *Exp Clin Psychopharmacol, 13*, 41-47.

Rose, G.L. Skelly, J.M., Badger, G.J., Naylor, M.R. & Helzer, J.E. (2012). Interactive Voice Response (IVR) for Relapse Prevention Following CBT for Alcohol Use Disorders: A Pilot Study. *Psychol Serv, 9*, 174-184 [Special section on technology-based mental health services].

Rose, G.L., MacLean, C.D., Skelly, J., Badger, G.J., Ferraro, T.A., et al. (2010a). Interactive voice response technology can deliver alcohol screening and brief intervention in primary care. *J Gen Intern Med, 25*(4):340-4.

Rose, G.L., Skelly, J.M., Badger, G.J., MacLean, C.D., Malgeri, M.P., et al. (2010b). Automated screening for at-risk drinking in a primary care office using interactive voice response. *J Stud Alcohol Drugs, 71,* 734-738.

Rosen, M.I., Wallace, E.A., McMahon, T.J., Pearsall, R., Woods, S.W., et al. (1994). Buprenorphine: duration of blockade of effects of intramuscular hydromorphone. *Drug Alcohol Depend, 35*, 141–149.

Rosenthal, R.N., Ling, W., Casadonte, P., Vocci, F., Bailey, G.L., Kampman, K., Patkar, A., Chavoustie, S., Sigmon, S.C., Blasey, C. & Beebe, K.L. (in prep). Buprenorphine implants for treatment of opioid dependence: Randomized comparison to placebo and sublingual buprenorphine/naloxone. *Addiction*.

Rounsaville, B.J. & Kosten, T.R. (2000). Treatment for opioid dependence: Quality and access. *JAMA*, *283*(10):1337-1339.

Schwartz, R.P., Highfield, D.A., Jaffe, J.H., Brady, J.V., Butler, C.B., et al. (2006). A randomized controlled trial of interim methadone maintenance. *Arch Gen Psychiatry, 63,* 102-109.

Schneider, M.F., Bailey, J.E., Cicero, T.J., et al. (2009). Integrating nine prescription opioid analgesics and/or four signal detection systems to summarize statewide prescription drug abuse in the United States in 2007. *Pharmacoepidemiol Drug Saf, 18(*9), 778-790.

Schwartz, R.P., Jaffe, J.H., O'Grady, K.E., Kinlock, T.W., Gordon, M.S., Kelly, S.M., et al. (2009b). Interim methadone treatment: Impact on arrests. *Drug Alcohol Depend, 103*, 148-154.

Schwartz, R.P., Jaffe, J.H., Highfield, D.A., Callaman, J.M., & O'Grady, K.E. (2007). A randomized controlled trial of interim methadone maintenance: 10-Month follow-up. *Drug Alcohol Depend, 86*, 30-36.

Schwartz, R.P., Jaffe, J.H., O'Grady, K.E., Das, B., Highfield, D.A., & Wilson, M.E. (2009a). Scaling-up interim methadone maintenance: Treatment for 1,000 heroin-addicted individuals. *J Subst Abuse Treat, 37,* 362-367.

Schwartz, R.P., Kelly, S.M., O'Grady, K.E., Gandhi, D., & Jaffe, J.H. (2011). Interim methadone treatment compared to standard methadone treatment: 4-month findings. *J Subst Ab Treat*, 41, 21-29.

Searles, J.S, Helzer, J.E., Rose, G. L., & Badger, G.J. (2002). Concurrent and retrospective reports of alcohol consumption across 30, 90, and 366 days: Interactive Voice Response compared to the Timeline Follow Back. *J Stud Alcohol, 63*, 352-362.

Secades-Villa, R., García-Rodríguez, O., García-Fernández, G., Sánchez-Hervás, E., Fernandez-Hermida, J.R., et al. (2011). Community reinforcement approach plus vouchers among cocaine-dependent outpatients: Twelve-month outcomes. *Psychol Addict Behav, 25*(1), 174-179.

Secades-Villa, R., García-Rodríguez, O., Higgins, S.T., Fernández-Hermida, J.R., & Carballo, J.L. (2008). Community reinforcement approach plus vouchers for cocaine dependence in a community setting in Spain: Six-month outcomes. *J Subst Abuse Treat, 34*(2), 202-207.

Selzer, M.L. (1971). The Michigan Alcoholism Screening Test: The quest for a new diagnostic instrument. *Am J Psychiatry, 127*, 1653-1658.

Shah, N.G., Lathrop, S.L., Reichard, R.R., & Landen, M.G. (2008). Unintentional drug overdose death trends in New Mexico, USA, 1990-2005: Combinations of heroin, cocaine, prescription opioids and alcohol. *Addiction, 103,* 126-136.

Sigmon, S.C. (2006). Characterizing the emerging population of prescription opioid abusers. *Am Journal Addict, 15* (3), 208-212.

Sigmon, S.C. (2008). Prescription drugs. In G.L. Fisher & N.A. Roget (Eds.), Encyclopedia of Substance Abuse Prevention, Treatment, and Recovery. California: Sage Publications, Inc., pp 695-698.

Sigmon, S.C. & Stitzer, M.L. (2005). Use of a low-cost incentive intervention to improve counseling attendance among methadone-maintained patients. *J Subst Abuse Treat, 29*, 253-258.
Sigmon, S.C., & Meyer, A.C. (in preparation). Utility of sustained-release buprenorphine formulations for treating opioid dependence: A web-based survey of physician opinion.
Sigmon, S.C., & Patrick, M.E. (2012). The use of financial incentives in promoting smoking cessation. *Prev Med, 55*, 24-32.
Sigmon, S.C., Bisaga, A., Nunes, E.V., O'Connor, P., Kosten, T., et al. (2012). Opioid detoxification and naltrexone induction strategies: Recommendations for clinical practice. *Am J Drug Alcohol Abuse, 38*(3), 187-99.
Sigmon, S.C., Correia, C., & Stitzer, M.L. (2004a). Cocaine abstinence during methadone maintenance: Effects of repeated exposure to voucher-based reinforcement and predictive utility for response to abstinence incentive interventions. *Exp Clin Psychopharmacol, 12*(4), 269-275.
Sigmon, S.C., Dunn, K., Saulsgiver, K., Patrick, M., Badger, G.J., et al. (2013). A randomized, double-blind evaluation of buprenorphine taper duration in primary prescription opioid abusers. *JAMA Psychiatry*. doi:10.1001/jamapsychiatry.2013.2216
Sigmon, S.C., Dunn, K.E., Badger, G.J., Heil, S.H., & Higgins, S.T. (2009). Brief buprenorphine detoxification for the treatment of prescription opioid dependence: A pilot study. *Addict Behav, 34*, 304-311.
Sigmon, S.C., Higgins, S.T. & Badger, G.J. (2000). Characterizing HIV/AIDS knowledge among cocaine-dependent outpatients. Paper presented at the 108th Annual Convention of the American Psychological Association, Washington, DC.
Sigmon, S.C., Moody, D.E., Nuwayser, E.S., & Bigelow, G.E. (2006). An injection depot formulation of buprenorphine: Extended biodelivery and effects. Addiction, 101, 420-432.
Sigmon, S.C., Patrick, M., Meyer, A.C., Heil, S.H., Badger, G.J. & Higgins, S.T. (in preparation). Maintaining smoking abstinence among patients receiving opioid agonist treatment with contingent voucher-based incentives.
Sigmon, S.C., Patrick, M.E., & Meyer, A.C. (in preparation). Characterizing barriers to ongoing opioid treatment among methadone-maintained patients in a rural state.
Sigmon, S.C., Wong, C.J., Nuwayser, E., Chausmer, A., & Bigelow, G.E. (2004b). Evaluation of depot buprenorphine: Placebo comparison. *Addiction, 99*, 1439-1449.
Sobell, L.C., Sobell, M.B., Leo, G.I., & Cancilla, A. (1988). Reliability of a timeline method: assessing normal drinkers' reports of recent drinking and a comparative evaluation across several populations. *Br J Addict, 83*, 393-402.
Sobel, B.-F.X., Sigmon, S.C., Walsh, S.L., Johnson, R.E., Liebson, I.A., et al. (2004). Open-label trial of an injection depot formulation of buprenorphine in opioid detoxification. *Drug Alc Depende, 73*, 11-22.
Stacy, J.N., Schwartz, S.M., Ershoff, D., & Shreve, M.S. (2009). Incorporating tailored interactive patient solutions using interactive voice response technology to improve statin adherence: Results of a randomized clinical trial in a managed care setting. *Popul Health Manag, 12*(5), 241-254.
Stitzer, M.L. & Sigmon, S.C. (2006). Other substance use disorders: Prevalence, consequences, detection and management. In: Strain EC, Stitzer ML, eds. *The Treatment of Opioid Dependence*. Baltimore, MD: The Johns Hopkins University Press, pp. 365-397.
Stotts, A.L., Dodrill, D.C., Kosten, T.R. (2009). Opioid dependence treatment: Options in pharmacotherapy. *Expert Opin Pharmacother, 10*(11):1727-1740.
Substance Abuse and Mental Health Services Administration (SAMHSA). (2006a). Diversion and abuse of buprenorphine: A brief assessment of emerging indictors. Final Report. http://buprenorphine.samhsa.gov/Buprenorphine_ FinalReport_12.6.06.pdf
Substance Abuse and Mental Health Services Administration (SAMHSA). (2006b). Diversion and abuse of buprenorphine: A brief assessment of emerging indictors. Results of the Vermont Case Study. http://buprenorphine.samhsa.gov /Vermont.Case.Study_12.5.06.pdf
Substance Abuse and Mental Health Services Administration. (2010). *Results from the 2009 National Survey on Drug Use and Health: Volume I. Summary of National Findings* (Office of Applied Studies, NSDUH Series H-38A, HHS Publication No. SMA 10-4856 Findings). Rockville, MD. http://oas.samhsa.gov/NSDUH/2k9NSDUH/2k9Results.htm
Sullivan, L.E., Barry, D., Moore, B.A., Chawarski, M.C., Tetrault, J.M., et al. (2006). A trial of integrated buprenorphine/naloxone and HIV clinical care. *Clin Infect Dis, 43*:S184-190.

Sullivan, L.E., Moore, B.A., Chawarski, M.C., Pantalon, M.J., Barry, D., et al. (2008). Buprenorphine/naloxone treatment in primary care is associated with decreased HIV risk behaviors. *J Subst Abuse Treat, 35*:87-92.

Tacke, U., Uosukainen, H., Kananen, M., Kontra, K., & Pentikäinen, H. (2009). A pilot study about the feasibility and cost-effectiveness of electronic compliance monitoring in substitution treatment with buprenorphine–naloxone combination. *J Opioid Manag, 5*, 321–329.

Treatment Episode Data Set (TEDS). (2004). National admissions to substance abuse treatment services: 1992-2002. DASIS Series: S-23, DHHS Publication No. (SMA) 04-3965. Rockville, MD.

Tetrault, J.M., Moore, B.A., Barry, D.T., O'Connor, P.G., Schottenfeld, R.S., et al. (2012) Brief versus extended counseling along with buprenorphine/naloxone for HIV-infected opioid dependent patients. *J Subst Abuse Treat, 43*:433-439.

Uosukainen, H., Pentikainen, H., & Tacke, U. (2013). The effect of an electronic medicine dispenser on diversion of buprenorphine-naloxone: Experience from a medium-sized Finnish city. *J Subst Ab Treat, 45,* 143-147.

Wall, T.L., Sorensen, J.L., Batki, S.L., Delucchi, K.L., London, J.A., et al. (1995). Adherence to zidovudine (AZT) among HIV-infected methadone patients: A pilot study of supervised therapy and dispensing compared to usual care. *Drug Alcohol Depend, 37*, 261-269.

Walsh, S.L., Preston, K.L., Bigelow, G.E., & Stitzer, M.L. (1995). Acute administration of buprenorphine in humans: Partial agonist and blockade effects. *J Pharmacol Exp Ther, 274*, 361-372.

Walsh, S.L., Preston, K.L., Stitzer, M.L., Cone, E.J., & Bigelow, G.E. (1994). Clinical pharmacology of buprenorphine: Ceiling effects at high doses. *Clin Pharmacol Ther, 55,* 569-580.

Warner-Smith, M., Darke, S., Lynskey, M., & Hall, W. (2001). Heroin overdose: Causes and consequences. *Addiction, 96*, 1113–1125.

Weiss, R.D., Potter, J.S., Provost, S.E., et al. (2010). A multi-site, two-phase, prescription opioid addiction treatment study (POATS): Rationale, design, and methodology. *Contemp Clin Trials, 31*(2), 189-199.

Wenger, L. D., & Rosenbaum, M. (1994). Drug treatment on demand – not. *J Psychoactive Drugs, 26,* 1−11.

Wish, E.D., Hoffman, J.A., & Nemes, S. (1997). The validity of self-reports of drug use at treatment admission and at followup: Comparisons with urinalysis and hair assays. *NIDA Res Monogr, 167*, 200-226.

Wisniewski, A.M., Purdy, C.H., & Blondell, R.D. (2008). The epidemiologic association between opioid prescribing, non-medical use, and emergency department visits. *J Addict Dis, 27*, 1-11.

Yancovitz, S.R., Des Jarlais, D.C., Peyser, N.P., Drew, E., Friedmann, et al. (1991). A randomized trial of an interim methadone maintenance clinic. *Am J PubHealth, 81,* 1185-1191.