Friends Research Institute

A Randomized Trial of Interim Methadone and Patient Navigation Initiated in Jail

Protocol

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Abstract

Opioid-dependent detainees frequently experience rapid relapse following release from jail and this relapse is associated with poor outcomes, such as continued illicit drug use, HIV infection, overdose death, crime, and re-incarceration. While community-based methadone maintenance (MM) has been proven effective and is in widespread use, to our knowledge, Rikers Island Jail in New York City is the only US jail in the past 25 years that routinely starts out-of-treatment detainees on MM and refers them to ongoing MM upon release. There are at least three barriers to starting MM programs (MMPs) in jails: (1) public officials remain unconvinced of the health, public safety, and economic benefits of MMPs, (2) a lack of funding for counselors in the jail; and, (3) the relatively low rates of entry and retention in treatment upon release reported from the Rikers program. This renewal application seeks to build on the parent grant entitled *"Entry into Comprehensive Methadone via Interim Treatment"* (2R01 DA 13636) as well as the results from two other completed NIDA-funded R01s conducted by the PI and his colleagues.

The parent grant found that newly-admitted MM patients who were randomly assigned to Interim Methadone (IM; methadone alone) during the first 4 months of MM had similar outcomes at 4- and 12-month follow-up as patients assigned to receive MM + counseling. A second study demonstrated the effectiveness of starting MM prior to release for inmates in prison (*not* jail). A third study found numerous barriers to MM treatment entry including lack of transportation, logistical problems with the admissions process, and lack of health insurance. The present application will test the impact of two relatively low-cost interventions that could increase treatment entry and retention post-release from jail, namely, IM and Patient Navigation (PN). PN, a strengths-based case management approach based on an existing manual adapted for this study, will help to link participants to treatment upon release

This is a three-group randomized clinical trial that will compare: IM+PN *v*. IM alone *v*. brief detoxification with methadone (enhanced treatment as usual). IM will be provided in jail to opioid-dependent detainees who were not in MM treatment at the time of arrest, with transfer to 1 of 4 MMPs upon release. Participants will be assessed at baseline, 1, 3, 6, and 12 months post-baseline in terms of drug use, HIV risk, criminal behavior, arrest, and re-incarceration. A cost-benefit analysis will provide the information policymakers need for evidence-based decision-making. Moreover, an adequate sample of women will permit an examination of differential response by gender to the interventions. Qualitative interviews will explore the specific barriers to treatment entry in the community. The proposed study will yield novel results that can be used to inform public policy in instituting more effective and cost-effective approaches to the problem of post-release relapse to opioid use in jail detainees. Data collection will be harmonized with two other randomized trials of extended release naltrexone for detainees being conducted by NYU (in New York City) and UCLA (in Albuquerque, NM) among detainees with opioid dependence to permit analysis to answer questions that cut across the three cooperative studies.

Background and Significance

Opioid dependence among arrestees is a major problem throughout much of the developed world.[40,41] Opioid-positive urine screening rates in major US city jails have ranged from 12% to 25%.[42] In Baltimore, where there were almost 58,000 arrestees in 2011, more than 2,600 male and 1,100 female jail detainees required opioid detoxification.

Post-release Relapse is Frequent and Risky

Relapse rates to opioid use upon release from jail are extremely high. One study of heroin-addicted inmates in Rikers Island found that 70% relapsed within one week of release and 90% within one month.[22] Recently-released inmates with opioid dependence face increased risk of overdose death,[1-3] and continued exposure to HIV[34] and hepatitis infection.[43] Relapse to heroin use undoubtedly plays a role in additional arrests, parole or probation violations, and return to incarceration.[44] Therefore, it is of considerable public health and public safety importance to develop approaches to engage arrestees in effective drug abuse treatment in the community and to assure continuity of care.

Methadone maintenance (MM) in the community has been shown in numerous RCTs,[6,45,46] multi-site longitudinal studies (DATOS, ATOS) and meta-analyses[7] to be effective in reducing opioid use. It has also been shown to reduce HIV risk behavior,[10] HIV sero-conversion,[13] and criminal behavior.[14,16] Although MM in *prison* for inmates serving sentences of varying lengths has been shown by the PI and his colleagues,[39] others in the US,[28] and in Australia[43], to be relatively effective in reducing relapse to opioid use, its use in *prisons* is unlikely to become widespread because prisoners have been incarcerated for extended periods of time and are no longer physiologically dependent. Further, MM started in *prison* does not address the critical population of 12.9 million individuals who rapidly cycle in and out of *jails* each year in the US.[47,48]

Jails Provide an Excellent Venue to Initiate Methadone Maintenance Treatment

According to a national survey of jails, opioid-dependent inmates who are not in MM at the time of arrest are rarely provided with MM,[49,50] despite rigorous RCTs and meta-analyses showing MM's effectiveness in the community compared to detoxification.[7] Most inmates do not even receive a community referral for any kind of continuing drug abuse treatment in the community upon release.[51] Because newly-arrested individuals experiencing acute opioid withdrawal are appropriately treated with an opioid agonist, initiating MM in *jail* would be much like doing so in the community. This circumstance is in contrast to doing so with prisoners with histories of opioid dependence who are no longer physiologically dependent on opioids, raising resistance from medical and corrections staff who do not believe such individuals should be started again on opioid agonists.

Methadone Maintenance Treatment is Rarely Provided in US Jails

While some US jails provide methadone to pregnant women[52] and a few, such as jails in Baltimore and Albuquerque, will continue MM at least temporarily for patients receiving MM in the community at the time of arrest,[53] the jail at Rikers Island in New York City is the only US jail of which we are aware that *initiates* MM for arrestees and inmates with short sentences.[54] Reports from that program over the last 19 years show that MM initiated in jail has the potential to improve patient outcomes. However, results to date leave much room for improvement in linking released inmates to treatment in the community.[20,22]

Barriers to Providing Methadone in Jails

In the US, there are a number of barriers to providing MM in jails. Correction officials may prefer detoxification to maintenance on philosophical grounds.[22,52] Another barrier is posed by federal and state regulations that require MM programs (MMP) to have a certain counselor-to-patient ratio. Thus, even those jails with medical services willing to provide MM (albeit only to individuals on MM in the community at the time of arrest) face the significant barrier of hiring drug abuse counselors for the program in an era of fiscal constraint. For example, in Philadelphia, the jail's MM provider was willing to provide MM for arrestees enrolled in MM at the time of arrest, but routinely placed such detainees on waiting lists for MM due to the lack of counselors.[21]

Interim Methadone Can Reduce Implementation Barriers to Jail-based Methadone Maintenance

The recent random assignment studies by the PI and his team showed that methadone with only emergency counseling (termed interim methadone; IM) over the first four months of community-based methadone treatment was as effective as MM with routine counseling as it is currently delivered.[25,26] This finding provides support for the provision of IM to out-of-treatment arrestees who are opioid-dependent at the time of incarceration. Building on these findings and those of others who also found no measurable effect of routine counseling on methadone treatment outcome,[55] the present study will utilize IM to overcome a major regulatory and financial barrier to initiating MM with detainees in opioid withdrawal who wish to enter MM.

Linkage between Jail and Community Drug Abuse Treatment is Often Unsuccessful

Beginning MM in jail is often not enough without effective linkage to post-release treatment which is considered essential for longer term benefit.[4] Many inmates started on MM in jail do not enter treatment in the community upon release. A recent clinical trial by Magura and colleagues conducted at Rikers Island Jail found that only 14% of study participants who started on MM actually entered MM in the community upon release.[20]

While earlier more optimistic longitudinal reports from Rikers found that approximately 50% of inmates who were started on methadone entered treatment in the community,[22,29] even this rate left considerable room for improvement. These investigators noted that the reluctance to enroll and remain in community MM upon release is a chronic problem.[56] This linkage problem occurs throughout Europe as well, where the provision of MM in jails and prisons is much more widespread than in the US.[4,57] There are no other published data from other US jails of which we are aware, since only the Rikers Program initiates MM during incarceration.

The low rate at which newly-released Rikers inmates started on MM make contact with the community clinic or their failure to successfully negotiate the clinics' admissions process[22,28,29] has led researchers and community MM staff to believe that such patients compared to typical treatment-seeking patients, need more concrete services such as help with obtaining tokens for public transportation, ID cards, and Medicaid.[22] Further, for those inmates who did enter MM treatment, early retention rates at 5 months were poor: 40% for men and 27% for women. Thus, patients transitioning from MM in jail to community treatment may need additional support to improve treatment retention rates. It is not clear why the retention rates for women were lower than those of men. More research is needed on the factors that influence retention for this population. It may be that some of those initiated on MM in jail may wish to transfer from one community MM program to another or to switch to buprenorphine treatment. Both possibilities are now available in Baltimore.

Patient Navigation Could Enhance Community Drug Abuse Treatment Entry and Retention

Patient Navigation (PN) provides one-on-one assistance to surmount barriers to entry and adherence with medical care for chronic disease. Originally designed to improve outcomes in oncology for disadvantaged female patients,[58] PN's conceptual foundation is a strengths-based case management perspective to help patients keep their appointments (through scheduling, reminders, and accompanying the patients), improve communication between the patient and their providers, offer health education, provide assistance with personal barriers to treatment (e.g., transportation, health insurance, childcare), and offer emotional support. Clinical trials have found that PN increased cancer screening and follow-up rates.[59] PN has been used to improve entry and adherence to HIV treatment.[31] Patients randomly assigned to PN had increased adherence to medical appointments and greater likelihood of achieving an undetectable viral load compared to controls.[60]

Addictions treatment studies have also found positive outcomes in randomized trials for services comparable to PN to increase the likelihood of treatment entry from: a central drug treatment intake;[61] receiving medical care at a hospital;[33] and community outreach.[62] Although a case management approach was not found effective in linking drug users, newly-released from *prison* to community treatment,[63] that study's sample was heterogeneous in terms of its drug use (only 10% were opioid-dependent) and did not receive pharmacotherapy. PN has not been studied in re-entry into the community with MM initiated in *jail*. It is our hypothesis that PN has the potential to assist newly-released detainees on MM to overcome barriers to successful community treatment entry. These barriers include: lack of transportation; lack of ID cards; lack of Medicaid or insurance coverage; the inability to navigate the treatment entry process; and ambivalence toward treatments.[22,47] The proposed study is also well-suited to determine costs and benefits of jail-based MM treatment, because it allows for the assessment of the relative costs of IM, IM with PN, and detoxification alone. The methodology for assessing benefits and costs for MM has been well-delineated.[64-66]

Gender Differences among Opioid-Dependent Jail Detainees

It has long been recognized that women who are opioid-dependent face barriers to treatment entry[67] and have service needs that differ from those of men.[68-70] Special individualized services such as PN, which has been used extensively with women for cancer screening, follow-up assessment, and treatment, have the potential to improve treatment entry and retention rates for women by addressing gender specific concerns,[71] such as offering their significant others drug addiction treatment referral[72-74] or making referrals for childcare or mental health treatment.[75] While the program initiating MM at Rikers Island has included women, the published data on outcomes for women in this treatment are sparse. In one study, women detainees were somewhat less likely than men to enter and remain in treatment following release.[22] There are almost no data providing guidance on what services or procedures would increase the likelihood of successfully remaining in treatment following release from incarceration or the relative benefits that might be associated with such success. It is well known that the patterns and severity of criminal offenses committed by women differ significantly from those of men,[73] yet relatively little is known about whether there are changes in the frequency of criminal behavior or the severity of offenses associated with entry and retention in MM post-release. Because more than 1,100 women are treated for opioid withdrawal in the Baltimore City jail each year, the present study is designed to recruit a significant number of women to answer these treatment and cost-benefit questions.

APPROACH

1. Progress Report

The parent grant consisted of an original R01 and a competing continuation which produced 14 published papers in high impact journals (see **Publication List**); these papers had lasting impact on the treatment system in Baltimore and beyond. The most salient studies and findings are briefly summarized below:

1.a. *Services Research on Interim Opioid Maintenance* (9/20/2001 – 7/31/2005). The original R01 was an RCT that compared IM to waiting list for 319 participants. The study had follow-up rates of 92.5% and 91.2% at 4-month and 10 months, respectively. Participants randomly assigned to the waiting list (treatment as usual at that time) were far less likely to enter standard MM and far more likely to continue to use heroin, commit crimes,[23,24] exhibit HIV sexual and drug use risk behavior while high,[76] and to be arrested (as determined by official arrest records).[18] Findings were widely disseminated at national research and practitioner meetings and featured in NIDA Notes and other secondary outlets.

1.b. *Scaling Up Interim Methadone* (7/15/2004 – 7/14/2005; CSAT grant). The PI and his team helped Baltimore's substance abuse authority (BSAS) to obtain a grant to expand IM at 6 MMPs to address ongoing waiting lists. During an 18-month period, over 1,000 patients were enrolled in IM, of whom 76.2% successfully transferred to standard MM.[77] For patients who transferred, opioid-positive tests decreased from 89.6% to 38.4% from admission to transfer. Following this project IM became a part of Baltimore's treatment system.

1.c. *Entry into Comprehensive Methadone Treatment via Interim Maintenance* (6/1/2007-5/31/2012). This competing continuation was an RCT conducted at two community-based MMPs. Adults on MMP waiting lists (*N* = 230) were randomly assigned to either 4 months of IM followed by 8 months of standard methadone (SM) or to SM for 12 months. At one site, a third condition, restored methadone (RM), was included in the random assignment; its counselor had half the number of patients as the counselors in the SM condition. Participants were interviewed at baseline, and at 2, 4, and 12 months post-baseline, assessing enrollment and retention in standard MM, heroin and cocaine use, self-reported HIV-risk, earnings, hospitalizations, criminal activities, and incarcerations. The follow-up rates for the IM, SM, and RM conditions were: 97.9%, 89.4%, and 96.3% at 4 months; and 93.9%, 88.5%, and 92.5% at 12 months.

Key Findings:

IM vs. Standard MM at 4 months. On an intent-to-treat analysis the three conditions differed significantly in the number of individual, group, and total counseling sessions. The IM condition received a mean (SD) of 0.7 (1.7) total counseling sessions, SM received 8.3 (4.8), and RM received 17.7 (5.5) sessions. Retention rates did not differ (91.9%, 80.8%, and 88.9%, for IM, SM, and RM, respectively). There were no significant differences among conditions over time in ASI composite scores, days of heroin or cocaine use, or heroin or cocaine positive urine drug tests.

IM vs. Standard MM at 12 months. Treatment retention rates for IM, SM, and RM groups were 60.6%, 54.8%, and 37.0% respectively. These differences were not significant. On an intent-to-treat basis, the conditions did not differ in ASI composite scores, heroin or cocaine positive urine drug tests, self-reported days of heroin or cocaine use, days of criminal activity, money spent on drugs, or arrests.[26]

HIV risk findings: Among the drug-injecting subsample (*n*=110) there were significant decreases over time in frequency of injecting and sharing injection equipment and among the sample who reported unprotected sex at baseline (*n*=130), there were decreases in reports of having sex without a condom either with someone who was not a spouse or primary partner or having sex while high. There were no treatment condition by time interaction effects for any of the HIV-risk behaviors at the 4-month assessment.[27]

Cost-benefit findings: Participants were relatively high consumers of high-cost hospital and ER facilities and there appeared to be little or no impact by condition on the level of utilization. There were also no significant differences in arrests and days of incarceration in the 12 months post-random-assignment. Hence, the major difference in cost benefit among the conditions was the modestly lower cost for the IM condition. [78]

Parole and Probation Findings: Patients on probation/parole showed improvements in outcomes comparable to patients not on probation/parole, regardless of level of counseling during the first 4 months of treatment.[79] Taken together, these findings give us confidence that IM will be acceptable and effective for individuals in the criminal justice system.

The present proposal is a logical next step emanating from the major findings of the parent studies described above and the work of the PI and his colleague Timothy Kinlock that examined MM for sentenced prisoners (see **Background** above).[39] The use of PN in the present study will address many of the barriers to treatment entry and retention including logistical challenges at the programs, lack of transportation and insurance found in the PI's other NIDA-funded R01 study of methadone treatment entry and retention.[25,80-84]

Dissemination: The parent grant has produced 14 publications (10 of which were during the last competing renewal period), including papers in the *Archives of General Psychiatry, Addiction, Drug and Alcohol Dependence,* and the *Journal of Substance Abuse Treatment.* Our work has been listed on SAMHSA's National Registry of Evidence-based Practices,[85] the National Institute of Justice's website of evidence-based practices,[86] and the Agency for Healthcare Research and Quality's website for innovative practices.[87] During the last competing continuation period, investigators presented study findings to local, State and Federal

officials and at scientific and treatment provider conferences, including 4 consecutive meetings of the College on Problems of Drug Dependence (7 posters and 1 oral presentation); 4 consecutive meetings of the Addiction Health Services Research (4 posters and 1 oral presentation); the American Academy of Addiction Psychiatrists (1 poster); 2 workshops at the American Psychiatric Association; 2 Annual Meetings of the American Association for the Treatment of Opioid Dependence; 1 oral presentation at the National Conference on State Legislatures; 4 workshops at National Judicial College Trainings; oral presentations at the NIDA Intramural Research Program and NIDA's DESPR; and three hospital grand rounds. The PI has made oral presentations at NIDA's request at four international symposia in Argentina, Egypt, Italy, and Russia.

Investigators. The PI, Dr. Robert Schwartz, has been the Medical Director of Friends Research Institute (FRI) for the past 13 years. He has served as PI on 5 R01 grants, is Co-PI of the CTN's Mid-Atlantic Node, and has over 80 peer-reviewed publications. One of the hallmarks of his team's efforts has been to conduct RCTs that have had sustained impact on the field. For example, findings from the parent grant led to the adoption of IM as part of Baltimore's treatment system. His collaboration on the RCT of methadone for prisoners contributed to the opening of an MMP in the Baltimore City jail for individuals in MM at the time of arrest (see **Biosketch**).

Co-I Dr. Jerome Jaffe has conducted pivotal studies with LAAM, methadone, and buprenorphine and has over 200 publications. He has been collaborating with PI Schwartz for over 10 years on their studies of IM and is particularly well-suited to serve as Co-I (see **Biosketch** and **Budget Justification**).

Co-I Dr. Shannon Gwin Mitchell is a community psychologist with expertise in process evaluations and qualitative research in drug addiction and HIV risk behavior. She was PI on our team's RCT comparing intensive outpatient to outpatient counseling among 300 African Americans treated on buprenorphine.[88] She is leading the qualitative component of the NIDA-funded CJ-DATS study examining approaches to increasing the use of medications in parole and probation. She is well poised to lead the study's process evaluation.

Co-I Dr. Sharon Kelly has been collaborating with Drs. Schwartz, Jaffe, and Mitchell for over 10 years. She served as Co-I and project manager on the parent study and oversaw the research assistants who achieved over 90% follow-up rates. Co-I Kelly also works closely with Dr. Kevin O'Grady, the project statistician. The latter has over 150 publications and has collaborated with the team for over a decade.

Co-I's Drs. Dunlap and Zarkin have extensive experience conducting economic evaluations of drug and alcohol treatment interventions including methadone treatment programs. They have estimated the costs of specific treatment services including MM,[89-91] and lifetime costs and benefits associated with MM[92] and are collaborating with the research team on the PI's ongoing R01 study of Reengineering Methadone Treatment.

Environment*:* Friends Research Institute (FRI) is well-suited to support the present application, which builds upon prior research conducted over the past 30 years in Baltimore (see **Facilities and Resources** for further description). FRI is currently conducting seven NIDA-supported studies relevant to the present proposal: 1) Buprenorphine for Prisoners; 2) Naltrexone for Probationers; 3) Criminal Justice Drug Abuse Treatment Study; 4) A Randomized Trial of Intensive Outpatient vs. Outpatient Treatment for African Americans Receiving Buprenorphine Treatment; 5) Entry into Comprehensive Methadone Treatment via Interim Maintenance; 6) SBIRT in New Mexico; and, 7) a participant organization in the Clinical Trials Network

Collaboration with the Department of Public Safety and Correctional Services (DPSCS): The PI has a long history of collaborating with the Maryland's DPSCS, which strongly supports the proposed study (see **Letter of Support**). He has served as Co-I on 4 NIDA-funded studies of medications for the treatment of opioid dependence (PI Kinlock) among individuals in prison and on parole or probation in Maryland. These studies have included MM for prisoners, buprenorphine for prisoners, naltrexone for probationers, and the CJ-DATS study of an organizational intervention to increase the use of pharmacotherapy for probationers and parolees.

Collaboration with Baltimore's Methadone Programs: The investigative team has worked closely with the four Baltimore MMPs that will be participating in the proposed research. Man Alive and Glenwood are part of the Mid-Atlantic Node of the CTN. REACH Mobile Health, Daybreak and the other two MMPs were study sites for the PI's current and/or previous NIDA-funded studies. [70,82-84,93-96] In addition, the city's substance abuse authority, Baltimore Substance Abuse Systems (BSAS), and Maryland's Health Department and Alcohol and Drug Abuse Administration strongly support the proposed study (see **Letters of Support**).

Specific Study Methods

We are proposing a 3-group RCT in which 300 opioid-dependent adults (150 males and 150 females) being treated for opioid withdrawal in the Baltimore City jail will be randomly assigned to receive either: (1) interim methadone with patient navigation (IM+PN); (2) IM without Patient Navigation (IM alone); (3) or enhanced treatment-as-usual (ETAU) including a brief methadone detoxification. Participants will be assessed at baseline, and 1-, 3-, 6-, and 12-months post-release to determine: entry and retention in treatment post-release; illicit opioid and cocaine use; DSM-5 criteria for opioid and cocaine use disorders; criminal behavior, arrests, and incarceration. Importantly, changes in HIV risk behavior will be determined. Finally, we will conduct cost, cost-effectiveness, and cost-benefits analyses.

1. Study Design Issues

We considered three issues in designing our study: (1) using alternative medications (buprenorphine or extended-release naltrexone) rather than methadone; (2) whether to include detoxification as an active comparison treatment; and, (3) whether to combine detoxification with PN. Although buprenorphine, a partial mu opioid agonist, could be used in jails and prisons with less regulatory and storage security burdens than methadone, it has a number of attributes that make its use in jails less desirable than methadone. First, it is more expensive than methadone, an important consideration for corrections departments that often have limited healthcare budgets. Second, buprenorphine is much easier to divert during treatment than methadone because it must be administered sublingually, and if diversion is to be minimized, the patient must be observed for 5-10 minutes until the dose is absorbed (in tablet or film form). In our ongoing prison study of buprenorphine,[97] more than 10% of participants attempted to divert the medication and hence were discontinued from the medication, a buprenorphine diversion rate similar to that found by Magura and co-workers in New York.[20] Where there are many patients,[20] buprenorphine could be used to advantage in smaller jails but is impractical in large urban jails. For these reasons, we have chosen to study methadone. In any case, findings on facilitating of post-release transition to MMPs associated with the use of PN may well be generalizable to other treatments such as buprenorphine, XR-NTX, and other medications now under development for opioid dependence.

We decided not to include extended release naltrexone (XR-NTX), because its cost currently is prohibitive and because, unlike XR-NTX, methadone is widely available in community treatment programs throughout Baltimore and elsewhere in the US for continuing care post-release. We decided to include a detoxification arm as a comparison because virtually all jails in the US (including in Baltimore) use detoxification as their "treatment as usual." In doing so we will be affording a less distressing detoxification regimen (using methadone rather than clonidine) for the treatment-as-usual condition in Baltimore City (and elsewhere) because clonidine is considered inferior to methadone for symptom relief.[98] We decided that combining PN with detoxification was impractical because newly-released opioid-dependent detainees not on opioid agonists at the time of release, unlike those in the IM+PN and IM alone conditions who will be on medication and referred to one of 3 particular programs, would be very difficult for the PNers to track, engage, and link to the many different types of treatment programs available in Baltimore City. Finally, to maximize human subject protection and to exceed the services typically offered in jails, all study participants will be provided with enhanced treatment-as-usual (ETAU) including substance use, overdose and HIV prevention information, as well as Baltimore's Behavioral Health Systems central telephone intake and assessment line, to reduce their risk of relapse (see **Human Subjects**).

2. Study Sites

Baltimore City Pretrial and Detention Services. The Baltimore City Pretrial and Detention Services is a Division of Maryland's Department of Public Safety and Correctional Services (DPSCS). It operates three facilities on its downtown campus in Baltimore City including Central Booking, where all arrestees in Baltimore City are brought by police and the Men's and Women's Detention Centers (the sites of the proposed study). Annually, there are 57,925 arrestees (not unduplicated) that pass through Central Booking for processing and transfer to the Men's and Women's Detention Centers. The Men's Detention Center has 2,684 beds and the Women's Detention Center has 861 beds. The average length of stay in the Detention Centers is 42 days and individuals who are sentenced for more than a few months are transferred to prisons elsewhere.

3. Participants in the Proposed Research

A total of 300 adult inmates (150 males and 150 females) will be enrolled in the study. We anticipate that participant characteristics will mirror the characteristics of the Baltimore City jail population from calendar year 2011, during which time there were 57,925 arrestees of whom 89% were African American, 10% were White, and 1% were other race; their mean age was 33. The majority of participants will be heroin-dependent; however, a small percentage are likely to be prescription opioid-dependent. In 2011, there were 2,622 men and 1,129 women (about 72 per week) who were not in opioid agonist treatment in the community at the time of arrest and who received opioid detoxification treatment in the Detention Centers with non-opioid medications. Given the large numbers of detainees receiving detoxification, it should be quite feasible to enroll 3-4 participants per week (less than 4% of the men and about 9% of the women who are treated for opioid withdrawal) and hence to complete participant recruitment in approximately 22 months.

3.a. Inclusion Criteria: (1) Meets DSM-5 criteria for opioid use disorder; (2) detained for at least 48 hours (because those detainees who are released quickly are most often released within 36 hours and hence would not have time to receive services in the study); (3) receiving opioid withdrawal treatment (as-usual) through the Detention Center's medical providers; (4) able and willing to provide informed consent in English; (5) detained for a charge that, if found guilty, will likely result in a sentence of less than 1 year; (6) plan to reside in Baltimore upon release; (7) 18 years of age and older.

3.b. Exclusion criteria: (1) enrolled in MM or buprenorphine treatment in the community at the time of arrest; (2) having a medical (liver failure, congestive heart failure) or psychiatric condition (e.g., suicidal ideation,

psychosis) that would make participation unsafe in the judgment of the medical staff or the PI; (3) pregnancy; (4) allergy to methadone; and, (5) requiring treatment for alcohol or sedative hypnotic withdrawal (i.e., in response to moderate or severe withdrawal).

3.c. Process Evaluation Subsample: Because the PN process in this study is a significant, innovative feature in terms of its relevance to both successful treatment entry upon release from jail (**Aim 1**), as well as its potential differential impact on women within this population (**Aim 2**), we will conduct a qualitative examination of the PN process. Out of the sample of 300, 32 participants (8 men and 8 women in the IM+PN condition, and 8 men and 8 women in the IM alone condition) will complete semi-structured interviews at 1 and 3 months post-jail release (see **Process Evaluation**). In addition, PNers will complete semi-structured interviews during Year 2 of the study to examine successes and barriers across their participant population.

4. Inmate Flow at Entry into Detention

Upon arrival at the Baltimore City jail complex, all newly-arrested adults are seen by a nurse for medical triage. The nurse notes if the arrestee is at risk for opioid (or alcohol or benzodiazepine) withdrawal. Inmates receive a physical exam within 24 hours of arrest, at which time they are tested for syphilis and offered HIV testing (which over 60% accept), and the women are tested for pregnancy. During either triage or the intake physical, treatment of opioid withdrawal can be instituted. Inmates whose opioid withdrawal begins (or worsens) after this time may subsequently request a sick call for opioid withdrawal or other reasons. During these visits, the medical staff routinely administers the Clinical Opioid Withdrawal Scale (COWS).[99]

4.a. Opioid detoxification as usual

The Baltimore City jail has two physicians who have addiction medicine certification from the American Society of Addiction Medicine. Detainees not enrolled in community MM or buprenorphine treatment who experience opioid withdrawal are examined and treated symptomatically with clonidine, compazine, tylenol, phenergan, and/or other over-the-counter medications for several days as needed. Nurses monitor the patient's vital signs and administer the medications to the patients several times per day. In some cases (e.g., more severe opioid withdrawal), at the discretion of the medical staff, brief methadone detoxification can be instituted.

4.b. Recruitment

During the first days of opioid withdrawal treatment, medical staff providing opioid detoxification will inform patients about the present study and invite them to speak with the research assistant (RA) if they wish to hear about the study. The RA, who will be onsite at the Detention Centers 5 days per week, will speak with interested inmates in a private room to describe the study to assess interest and to screen for eligibility. The RA will generally spend 2 days in the Men's and 2 days in the Women's Detention Center per week if necessary and will spend the remaining day at the Detention Center that did not recruit the target number of participants. Individuals who screen eligible will be offered an initial informed consent that will include giving consent to obtain their official arrest records at the conclusion of the 12 month follow-up period. The consent will describe the risks and benefits of participation and will include information about alternative treatment options for those not interested in participating (see **Human Subjects**). Alternative options that are available at the jail include completing the detoxification as usually prescribed by the medical staff (see **Section 4.1. opioid detoxification**), and, upon release, entering any of several drug abuse treatment programs in the community (if they chose to do so). Individuals refusing participation will be provided with the contact information of the Baltimore Behavioral Health Systems help line that provides assessment and treatment referral over the phone. A consent quiz will be administered to potential study participants up to three times until a score of 100% is achieved. Potential participants unable to score 100% on the quiz will not be eligible for participation. For logistical reasons, once a target of no more than 3 men and 3 women have consented and entered the study in any given week, no more participants will be enrolled that week. We will recruit five days per week, if necessary.

5. Random Assignment

After providing informed consent and completing a baseline assessment (see **Measures**, below), participants will receive information about HIV prevention, overdose prevention, and substance use and then will be randomly assigned to 1 of the 3 study conditions: 1) IM with PN; 2) IM alone; or, 3) enhanced treatment-as-usual (ETAU), including Methadone Detoxification. Participants will be assigned to conditions using a random permutation procedure, such that, within gender, for each block of 3, 6, or 9 participants, ⅓rd will be assigned at random to the IM with PN Condition, ⅓rd to the IM alone condition, and ⅓rd to the ETAU condition, ensuring that both male and female participants have an equal chance of being assigned to each of the 3 conditions. [Random block sizes will be used in order to thwart any attempt by an interested observer, such as a staff member, to deduce the random assignment procedure.] Sealed opaque envelopes will be prepared for the project RA at each detention center based on this random permutation procedure. The RA will open the

designated envelope and inform the participant to which one of the conditions s/he has been assigned. Only the project manager and PI will have access to the random assignment table.

6. Study Conditions

6.a. Methadone Detoxification (Enhanced Treatment-as-Usual)

Methadone detoxification will be provided by the medical team at the jail. All methadone provided in the jail is directly administered by the nursing staff. Medical staff will discontinue treatment as usual (clonidine, etc) for participants assigned to methadone detoxification and will begin typically with up to 30 mg methadone on the first day, which can be increased by 5 mg per day up to a maximum of 40 mg in response to the daily administered COWS scores. Once a stable dose has been achieved at which the participant is comfortable, it will be decreased by 5 mg per day. It is anticipated that detoxification will last an average of 7-10 days. This Enhanced Treatment-as-Usual Condition will also include substance use information and substance use treatment referral, HIV prevention information, and overdose prevention information. The research assistant will provide the participants assigned to this Condition with the contact information for the Baltimore City behavioral health authority's (Baltimore Behavioral Health Systems) telephone assessment and referral help line (see **Letter of Support** from Baltimore Substance Abuse Systems). This help line provides telephone screening and referral to a wide range of publicly-funded drug abuse treatment and harm minimization services (overdose prevention and needle exchange), and 12-step meetings in Baltimore. In summary, this condition will be superior to the detoxification-as-usual afforded to arrestees because participants will receive detoxification with methadone rather than clonidine and other non-opioids, and they will also receive the central intake and referral number for substance use treatment and harm minimization services in Baltimore, as well as information about overdose prevention, HIV risk prevention, and substance use.

6.b.Interim Methadone Maintenance without Patient Navigation (IM alone)

IM will be provided by the medical team at the jail. Methadone dosing will be individualized, although it will generally be started at 20 – 30 mg per day and increased by 5 mg every other day (at the request of the participant and with medical staff approval) to a target of approximately 60 mg. Participants will be administered methadone under direct observation by the nurse at the methadone dispensaries in the Men's and Women's Detention Centers. IM participants will continue in treatment in the jail until their release. Should they require discontinuation of methadone due to unwanted side effects, transfer to another facility (e.g., for behavioral reasons or due to sentencing), rule infractions (e.g., attempted diversion of methadone), or simply a request to discontinue, whenever possible, the participant will undergo a gradual dose reduction under medical supervision. Participants will not receive routine drug abuse counseling during incarceration. However, participants will be afforded those routine psychosocial treatments available to all inmates including those inmates undergoing detoxification-as-usual who are not enrolled in the study. These services include emergency and routine mental health consultation and treatment and case management to assess post-release needs for community referrals. Nursing staff will inform the participant about the four MMPs in the community that are participating in the study and willing to accept IM participants at the time of release so that participants can choose from among them.

6.c. Interim Methadone Maintenance with Patient Navigation (IM+PN)

Participants will receive IM in the Detention Center as described above. In addition, PN will be provided for up to three months post-release. The PI, who has extensive experience with MM treatment and with MM in prison, and supervised case management as part of a recent RCT,[100] will be trained by PI Schwartz and consultant Sorensen (see **Letter of Support**) in Dr. Sorensen's intervention that successfully linked heroin-dependent patients receiving medical care at San Francisco General Hospital to community MMPs.[33] The PN staff will be trained by the PI over the first two weeks of the study and will employ patient navigation which includes strengths-based management[101,102] that will provide assessment, linkage to treatment, care coordination, patient advocacy, and monitoring. The manual used in the study by Sorensen (see **Appendix 1** and **2**) will be modified by the study team for Baltimore and for jail reentry.

PNers will meet with the participants assigned to the IM+PN Condition prior to their release and obtain detailed contact information from the participant. A community care plan will be developed with the inmate, including a discussion about how to select which of the four MMPs the participant wishes to attend upon release. The PNers will coordinate this decision with nursing, so that the nurses may make arrangements to transfer the participant's records to the receiving program. Because detainee releases can occur at any time of the day, the PNers will provide the participants with their cell phone and office numbers and encourage participants to call them upon release. The PNers will also routinely check the roster of the detention center to identify any individuals who have been released and will reach out to ensure contact with newly-released inmates through the detailed contact information collected at baseline.

PN services will be focused on facilitating entry into community-based drug abuse treatment and addressing barriers to re-entry and retention in treatment. These barriers may include difficulty obtaining appointments at community-based MMPs, challenges interacting with clinic staff, transportation (obtaining bus

passes), housing challenges, and fluctuating motivation. Gender-specific issues will be addressed, such as obtaining child care and referrals to treatment for drug using significant others. PNers will arrange to meet the participant at the selected MMP for the first visit to maximize the likelihood of keeping the appointment. PNers will remain with the participant during the intake process to assist in communication with the MMP if necessary and to advocate for the participant. They will also facilitate keeping treatment appointments through reminders, coaching, and if necessary, meeting the participant either at the MMP or in the community to accompany them. The PNers will call participants who miss appointments to determine what happened and to facilitate another appointment or referral. PNers will seek out participants if they cannot be reached by phone (much the same way that our research staff now does for follow-up interviews using extensive locator information).

Once a participant is enrolled in treatment, the PNer will assist them (if necessary) in gaining an ID card and will provide them with bus or train tokens for the first few weeks until a reduced fare bus pass can be obtained. If necessary, navigators will assist the participant in complying with the instructions provided by the clinic staff in completing required documentation to obtain Medicaid or Maryland's state health benefits that will pay the clinic for treatment, whether MM or some other modality. Limited funds will be available for the PNers to obtain bus tokens, and to pay for ID cards and other needed low-cost services.

It is anticipated that the PNers will meet with the participants weekly during the first month, and about every other week (or more) during the second and third months, as needed. Phone calls will be made in between appointments or used as reminders or to seek the participant out if appointments are missed.[103] As needed, the PNers will go into the community to find the participant at their home or usual hangouts to try to reengage them following the procedures that we use successfully in tracking this population for research follow-ups. The PNers will enter in an excel database and written progress notes all of their participant-related activities including all attempts at contacting participants, PN services delivered, site of PN services, referrals made, and community services received.

Adherence to the PN model will be checked by the PI, who will meet weekly with the PNers for supervision and quality assurance activities which will include review of participant databases and written notes. Supervision will also serve to troubleshoot problems in accessing community services and treatment entry. PNers may be either two half-time employees each having an average caseload of 8 participants, which is an average caseload for this type of service, or one full time PN, who would have an average caseload of 16 participants.

6.d. Referral to Ongoing Methadone Maintenance Treatment in the Community

The Detention Center's MMP staff will fax the participant's assessment and physical exam, laboratory test results, and dosing information to the one of the selected receiving community-based MMPs. This procedure has been successfully followed for the past three years for patients who were enrolled in MM at the time of arrest (see **Letter of Support** from BSAS) and permits a seamless transition to the selected community program. For participants in the IM+PN condition, the PNers will assist in the transmission of the above-described information in cases in which the transfer of clinical information was unsuccessful.

IM+PN and IM alone participants will be told by the RAs and navigators to report to their MMP on the day following release even if it is a Sunday. The Detention Center will arrange courtesy dosing at the community-based MMP (as would occur on a trip to another state) until the participant can be seen by the receiving MMP for an intake. For the purpose of the study, the community-based MMP will admit the participant assigned to IM conditions for continued methadone treatment if the participant arrives within 3 days of release. The clinic may schedule the patient to see the clinic medical staff for re-evaluation but this will not delay the continued medication. The MMPs' intake counselor will review the chart supplied from the Detention Center and meet with the participant for an intake assessment.

7. Research Interviews

Research interviewers will conduct follow-up interviews at 1-, 3-, 6-, and 12-months post-release using time line follow-back techniques[104] that we have successfully employed in our previous research.[23-26]

Follow-up and Attrition: Consistent with the parent study[25,26] and our prior research with opioid-dependent patients[23,24] we will collect detailed locator information, including cell phone numbers (for calls or texts), contact information for relatives and peers, and names and addresses of participants' "hang-outs." We will also, with permission of the participant, collect email addresses and social media contact information (e.g., facebook; Twitter) in order to contact the participant. When unable to contact participants via phone, the RAs will track the participants in the community through our successful and robust procedures for participant tracking. Thus, we expect to obtain follow-up rates of about 90%, consistent with our previous studies in Baltimore City with out-of-treatment opioid dependent individuals[23,24,105] and the parent study.[25,26] The PI and his staff have located over 90% of participants at 10-month follow-up for the first study of Interim Methadone, and at 12 months in both the parent study, and in the RCT of methadone for prisoners.[39]

Measures: Figure 1 shows a schedule of the measures corresponding to each study aim.

Figure 1. Data Collection Schedule and Measures by Aim

Measures	Baseline	Follow-up
Aims 1-2: To compare IM + Patient Navigation *v*. IM alone *v*. Methadone Detoxification (Enhanced Treatment-as-Usual) on: treatment entry and retention, illicit opioids and cocaine use, DSM-5 criteria for opioid and cocaine use disorders; HIV-risk behaviors, criminal activity, arrest, and incarceration.		
Treatment Entry (self-report from Methadone Treatment Exposure form))		1 month
Enrolled in Treatment (self-report from Methadone Treatment Exposure form)*		3, 6, & 12-month
Illicit Opioid and Cocaine Use (ASI and urine drug testing)	◆	1,3, 6, & 12-month
DSM-V Criteria of opioid and cocaine use disorder (modified WMH CIDI)	◆	3- 6, and 12-month
Criminal Behavior (ASI)	◆	1,3, 6, & 12-month
Arrests and Incarcerations: Self report and criminal justice records	◆	12-month
HIV Risk Behavior (RAB)	◆	6, & 12-month
Overdose AE Form		1,3, 6, & 12-month
Methadone Treatment Exposure Questionnaire		1,3, 6, & 12-month
Quality of Life (WHOQOL-BREF)	◆	1,3, 6, & 12-month
Aim 3: To conduct a cost-benefit analysis of the relative costs of the three study Conditions		
Economic Form 90 (Health care utilization)	◆	3, 6, & 12-month
Substance Abuse Services Cost Analysis Program (SASCAP)		†
Arrest and incarceration (Criminal Justice Records)	◆	12-months only

* Participants transitioning directly to other community MMPs or buprenorphine treatment will be considered still in treatment.
† Consistent with prior research, the SASCAP will be administered once during the treatment phase.

Participants will be paid $30 for follow-up interviews (regardless of whether they are conducted in the community or during a re-incarceration) and will provide consent for research staff to check hospital and arrest records. Participants who are interviewed for follow-up during a re-incarceration will have the option to receive their $30 deposited into their jail or prison account or to have a money order mailed to a designated person. They will not be paid for the baseline interview conducted in jail to avoid the perception of coercion.

Longer-term follow-ups: Participants will be asked (using a consent form addendum) if they'd be willing to have a 24-month follow-up interview for which they would be paid $40. The 24-month interviews will include the same assessments as the 12-month interviews described above. In addition they will be asked if the research team could contact them beyond the 24-month follow-up for further informed consent for even longer-term follow-up interviews.

Measures for Aim 1 and 2:

Entry into Treatment: within the first 30 days of release from jail will be obtained from patient self-report from the Methadone Treatment Exposure form.

Enrollment in Treatment: will also be obtained from self-report on the Methadone Treatment Exposure form.

Addiction Severity Index (ASI): assesses patient functioning through a 30-45 minute interview covering 7 key domains over the past 30 days including drug and alcohol use, legal, medical, psychiatric and employment status, family functioning and social relations.[106] Composite scores and items from each domain will be investigated (with particular emphasis on drug use and legal scores and items).

Urine Drug Testing: Urine samples will be collected by project staff at 1, 3, 6, and 12 months post-baseline and tested by an approved rapid drug test cup for opiates, methadone, buprenorphine, cocaine, and benzodiazepines. Results will be used for research purposes only and will not be shared with clinic staff.

Modified World Mental Health Composite International Diagnostic Interview (CIDI) for Drug Use Disorders Revised. The updated version of the CIDI-2[107] (termed the World Mental Health CIDI [www.hcp.med.harvard.edu/wmhcidi/index.php] will be used to determine whether individuals met the DSM-5 criteria for opioid and cocaine use disorders or remission during the one-month period prior to the 3, 6, and 12 month study assessments. The CIDI-2 was recommended by an expert panel of the NIDA CTN for gauging DSM-IV remission in clinical studies.[108] Its items can be used to determine DSM-5 criteria for substance use disorders. It will provide important and novel data that is complementary to self-reported drug use and urine testing data, and to the quality of life measurement, as an additional measure of change in functioning. It has been shown to have excellent reliability in diagnosing individuals with drug dependence.[109]

Arrests and Incarcerations: In addition to self-reports, the official arrest and incarceration records will be obtained for 1 year prior and 1 year post-study enrollment from the Maryland Department of Public Safety and Correctional Services. These records can be used to gauge the severity of offenses, which may change even when arrest frequency remains about the same. We have successfully obtained and analyzed data of this nature in previous research.[18]

Risk Assessment Battery (RAB): The RAB is a brief questionnaire composed of 45 questions covering substance use and sexual HIV risk behaviors that has been extensively used with drug-dependent populations.[13] The scale's drug-use risk and sex risk scores will be used as outcome measures.

World Health Organization Quality of Life (WHOQOL-BREF) is a brief 32-item instrument developed by the World Health Organization that has been used in a wide variety of populations internationally (Noerholm et al., 2004[109c]; WHOQOL GROUP, 1998[109d]; World Health Organization, 2004[109e]) and has been found to have strong psychometric properties (O'Carroll et al., 2000[109f]; Skevington et al., 2004[109g]). The WHOQOL-BREF produces scores in four QoL domains: physical, psychological, social, and environmental. The WHOQOL-BREF also contains a single item, which is not incorporated into any of the four scale scores, asking participants to rate their overall QoL on a 5-point scale from very poor to very good.

Methadone Dose: Higher methadone maintenance doses in jail have been shown to be related to higher rates of treatment entry following release from incarceration[22] and improved retention rates in community-based treatment.[46] As such, methadone dose will be recorded at release from the Detention Center and at each follow-up to permit an examination of the relationship between methadone dose and outcomes by treatment Conditions.

Overdose AE Form. This brief 12 item questionnaire was devised for the present study to examine the number and characteristics and responses to any non-lethal overdoses between study visits.

Methadone Treatment Exposure Questionnaire. This brief 7 item questionnaire was devised for the present study to examine methadone treatment status, anticipated length of sojourn in methadone treatment, and reasons for leaving treatment (if applicable).

Measures for Aim 3:

Economic Form 90: The Economic Form 90 survey has been modified for our ongoing research in MMPs and used successfully to collect data on participant outcomes and economic outcomes before, during, and after treatment. This instrument is useful to supplement the ASI whose time frame for follow-up interviews is restricted to the past 30 days for items such as arrest and hospitalization. The Economic Form 90 is a modified version of the Form 90 family of instruments that was originally designed to collect alcohol use and economic outcome data for alcohol treatment studies.[112,113] It will be used to collect data on residential drug treatment, outpatient, and emergency room health care utilization; criminal behavior including number of arrests, severity of offense, and nights incarcerated. Also collected will be labor market information including employment status, current wage, frequency of work, and amount of money received beyond paid employment (e.g., Social Security) and off-the-books earnings.

Substance Abuse Services Cost Analysis Program (SASCAP): Costs for each of the study conditions will be estimated using an activity-based costing approach which will allow cost estimation at the service level for study participants. To collect resource use and cost data necessary for activity-based costing, we will modify the SASCAP[90] to collect resource use and cost data for each condition necessary for activity-based costing. The SASCAP consists of a provider questionnaire administered once during the intervention phase to collect activity-level resource use and cost data for provider staff and nonlabor resources such as contracted services, building space, supplies and materials, and other miscellaneous resources (e.g., utilities). The SASCAP method reliably estimates the costs of specific treatment activities and the total cost per patient, and the investigators Dunlap and Zarkin have applied this micro-costing approach in other treatment studies.[66,89,114,115] If a significant number of participants transition from the initial MMP to another MMP or buprenorphine treatment, costs for these treatments will also be determined.

AIM 1. To determine the relative effectiveness of IM+PN *v*. IM alone *v*. brief methadone detoxification (enhanced treatment-as-usual [ETAU]) for opioid-dependent detainees at 1, 3, 6, and 12 months post-release in terms of: (a) post-release treatment entry and retention; (b) illicit opioid and cocaine use; (c) meeting DSM-5 criteria of opioid and cocaine dependence; (d) HIV-risk behavior; and (e) criminal behavior, arrest, and days of incarceration.

Hypothesis 1A: The IM+PN and IM Alone conditions will have higher rates of treatment entry and longer retention, and concomitant lower rates of illicit opioid and cocaine use and of meeting DSM-5 criteria for opioid and cocaine use disorders, HIV risk behavior, criminal behavior, arrests, and days of incarcerations than will the Methadone Detoxification [ETAU] condition.

Rationale: We are not aware of RCTs comparing treatment entry and retention rates for jail-based methadone maintenance (with or without PN) compared to detoxification. However, a longitudinal evaluation from Rikers Island has shown better treatment entry rates post-release for inmates started on MM rather than provided with detoxification[22] and MM has significantly higher treatment retention rates than methadone detoxification in non-incarcerated populations.[7] Therefore, we hypothesize that participants assigned to IM with or without PN are more likely to enter and remain in community-based treatment, and associated superior treatment outcomes.

Hypothesis 1B: The IM+PN condition will have higher rates of treatment entry and longer retention, and concomitant lower rates of illicit opioid and cocaine use, meeting DSM-5 criteria for opioid and cocaine dependence, HIV risk behavior, criminal behavior, arrests, and days of incarceration than will the IM Alone condition.

Rationale: Reports on the rates of entry into community-based MM treatment of inmates started on MM in Rikers Island range from 14%[20] to 50%[22] leaving considerable room for improvement. PN has been found to yield higher rates of treatment entry than no-PN in non-jail and non-prison samples of opioid-addicted adults.[33] We expect that PN, by reducing barriers to continued treatment in the community and re-engaging those who drop out over the first 3 months of MM, will result in the IM+PN condition having higher rates of treatment entry and longer retention in treatment, and associated superior treatment outcomes. [We are cognizant of the possibility that the effects may be attenuated at the 6-month and 12-month follow-up compared with the initial 3 month follow-up.]
AIM 2 To determine the relationship of gender to the relative effectiveness of treatment conditions.
Hypothesis 2A. Women in the IM+PN condition will have superior outcomes to men in the IM+PN condition in terms of (a)-(e), above; **Hypothesis 2B**: in contrast, women in the IM alone and methadone detoxification conditions will have poorer outcomes than men in the IM alone and methadone detoxification conditions.
Rationale: The few studies of reentry from incarceration that examined outcomes for opioid-dependent men and women started on MM have shown that women are less likely to enter and remain in treatment.[22] However, the PN literature shows that women respond well to this intervention.[116,117] Therefore, although we anticipate that women will have poorer outcomes than men in the IM alone and detoxification conditions, we hypothesize that women will respond better than men to IM+PN.

Analyses for Aims 1 and 2.

Intent-to-Treat Approach. All analyses will be conducted on available study-related data from all participants (based on their random assignment to treatment condition), regardless of whether or when they drop out of treatment.

Guiding Principle. Although the description of the statistical approach that follows is more in line with the language associated with a 'traditional' superiority trial, we endorse the "sensible formulation of the significance test" proposed by Jones and Tukey.[118] They outline an approach to significance testing that focuses not on the rejection of a null hypothesis, but on determining whether the data favor a determination of superiority or inferiority. As part of their approach, they suggest reporting not only a test statistic and its associated probability value but also a confidence interval and an effect size related to the determination of any difference. It would be our intention in reporting our results to adhere to Jones and Tukey's suggestions.

Outcome Variables. Outcome variables will be of three distinct types: 1) dichotomous variables (e.g., entry into treatment, illicit opioid and cocaine urine test results, meeting DSM-5 opioid and cocaine dependence criteria), assumed to follow a binomial distribution; 2) discrete random variables (e.g., number of days of heroin and cocaine use and criminal behavior in the past 30 days), assumed to follow a Poisson distribution; and, 3) continuous random variables (e.g., HIV Risk scale scores), assumed to follow a normal distribution. All distributional assumptions will be evaluated prior to the conduct of all analyses, and if such assumptions are not met, assumptions will be modified and statistical methods chosen accordingly, and/or outcome measures transformed appropriately. For example, it may be necessary to allow for under- or over-dispersion in the logistic and Poisson regression analyses; or a negative binomial model may be more appropriate for the count variables. [In the case of transforming an outcome variable, preference will be given to a transformation that permits clearer clinical interpretation of findings].

Explanatory Variables. The predictor variables in all statistical models can be categorized as either *Treatment Variables*, *Moderator Variables,* or *Control Variables*.

Treatment Variables: There will be a single treatment variable with three conditions: Intervention Condition [IM+PN *v*. IM Alone *v*. Methadone Detoxification (ETAU)].

Moderator Variables: There will be a single moderator variable: Participant Gender.

Control Variables: Three additional predictor variables – participant age, prior methadone maintenance treatment (yes *v.* no), and self-reported cocaine use at baseline – will be included as "main effects" in all analyses in order to examine for potential differences in treatment outcome as a function of these three variables. (In the parent study: 56% had never previously been in MM treatment; and, self-reported cocaine use at baseline predicted lower treatment retention at 6 months).

Time: Finally, the "repeated factor" in the statistical analysis of all outcome variables measured repeatedly will be assessment Time point, which will allow for the evaluation of both *differential course and impact* of the interventions as a function of the "between-subjects" Treatment Condition factor. (For information regarding which outcome variables are measured at what assessment time points, see **Figure 1. Outcomes and Measures by Aim** and **Measures**, above).

Planned Contrasts: It is possible to construct two orthogonal, single-degree-of-freedom, planned contrasts that directly test **Hypothesis 1A** and **1B**, respectively. Contrast 1A will compare the two IM treatment conditions (IM+PN and IM Alone, pooled) to the Methadone Detoxification condition. Thus, this comparison directly addresses the question of the differential effectiveness of some form of IM treatment in comparison to a 'minimally sufficient' treatment-as-usual (methadone detoxification). Contrast 1B will compare the IM+PN condition to the IM alone condition. Hence, this comparison directly addresses the question of the relative

effectiveness of the adding PN to IM treatment. Similarly, it is possible to construct two orthogonal, single-degree-of-freedom, planned contrasts that directly test **Hypothesis 2A** and **2B**, respectively. Contrast 2A will compare males and females in the IM+PN condition. Hence, this comparison directly addresses the question of the differential effectiveness of IM+PN treatment for males and females. Contrast 2B will compare males and females in the IM Alone and Methadone Detoxification conditions, pooled. Thus, this comparison directly addresses the question of the differential effectiveness of non-PN treatments for males and females. Given that both the course and impact of treatment are important to evaluate, planned contrasts can be examined both as each interacts with the "repeated factor" of Time (when there is a repeated factor), and as a "simple effect" at a given time point, in the event either Contrast X Time interaction effect proves to be significant.
AIM 3: To conduct a focused cost-effectiveness and cost-benefit study of the three treatment conditions
HYPOTHESIS 3a (Cost Hypothesis). IM alone will have greater treatment costs per person than detoxification. Furthermore, IM+PN will have greater treatment costs per person than IM alone.
HYPOTHESIS 3b (Cost-Effectiveness Hypothesis). IM+PN will yield better outcomes relative to the IM alone which in turn will yield better outcomes than detoxification in terms of higher rates of treatment entry and longer retention in treatment, and greater reductions in illicit opioid and cocaine use, decreased likelihood of meeting DSM-5 criteria for opioid and cocaine use disorders, decreased HIV risk behavior, and decreased criminal behavior, arrest, and incarceration. The better outcomes for IM+PN justify the greater costs of IM+PN compared to IM alone, making IM+PN cost effective compared to IM alone.
HYPOTHESIS 3c (Cost-Benefit Hypothesis). IM alone will yield greater economic benefit in terms of criminal activity, health care utilization, and employment in the 12-month post-release period relative to its costs relative to the detoxification condition. Furthermore, IM+PN will yield greater economic benefits than IM alone.
Rationale: By design, it is expected that IM+PN will require additional resources (e.g., labor, transportation expenses) relative to IM Alone and detoxification only due to the inclusion of PNers who are trained to facilitate enrollment in drug treatment for the participant as well as provide assistance in the early months of treatment. However, this additional case support is expected to yield better treatment entry and retention and, subsequently, improved outcomes. If these benefits exceed the additional costs, we would expect to find IM + PN to be cost-effective and cost-beneficial relative to the other 2 treatment conditions.

Statistical Method. A Generalized Linear Mixed Model (GLiMM) will be used to conduct all analyses.

Power. Stroup[119,120] has outlined a four-step procedure to estimate power for general linear mixed models, which can also be applied to generalized linear mixed models, and this procedure was followed to estimate power for the proposed study. From a more rudimentary and slightly less accurate perspective, assuming the primary outcome measures follow a normal distribution rather than Poisson or binomial distributions, power calculations based on the set correlation method[121,122] can be used to calculate effect sizes for desired power, including under the extremely conservative assumption that no other effect in the model is significant (with the resulting effect size estimates likely to be slight underestimates). For the sake of completeness, power calculations employ both perspectives.

Assuming α=.01 and *N*=300, the resulting SAS GLIMMIX power estimates (1 – β) for the four planned contrasts X Time (see *Planned Contrasts*, above; for retained in treatment and arrest and incarceration, the effect of interest was necessarily the four planned contrasts themselves, as there was no Time effect for this outcome) associated with **Hypothesis 1A**, **1B**, **2A**, and **2B** exceeded .81 in all cases, assuming "small" differences associated with each such effect, and even assuming an unstructured covariance matrix. For the set correlation approach, and in this case assuming *N*=270 due to attrition (see Follow-up and Attrition, above) in order to remain conservative, an effect size in the population associated with a Planned Contrast X Time for **Hypothesis 1A**, **1B**, **2A**, and **2B** of $\mathbf{f}^2$=.048 (.094 for retained in treatment and arrest and incarceration) would yield a power of .9 for that effect. [All 4 Planned Contrasts X Time for **Hypothesis 1A**, **1B**, **2A**, and **2B** have the same degrees of freedom, so yield a common effect size.] The effect size involving the Time effect falls in the "small" range, while the effect size that does not include a Time effect falls in the "small-to-medium" range, with $\mathbf{f}^2$=.02 considered a "small" effect and $\mathbf{f}^2$ = .15 a "medium" effect.[121]

9. Process Evaluation.
9.a. Need for Process Data: Due to the key role of PN in this study for overcoming barriers associated with community re-entry (**Aim 1**), particularly for women (**Aim 2**), we will conduct a qualitative process evaluation that will examine PN experiences in detail.
9.b. Qualitative Sample Selection: Using purposive sampling, a subset of 32 participants (16 IM+PN and 16 IM alone) will be selected to complete semi-structured qualitative interviews. Participant selection will emphasize heterogeneity in order to examine the views and experiences from as diverse a sub-sample as possible and will include an equal number of men and women from each condition. The proposed sample size will ensure that saturation is likely to be achieved (i.e., bringing new participants into the study until the data set is complete, as indicated by data replication or redundancy) and should allow for the extraction of thick, rich data

in which details concerning context and intention are included along with the facts.[123,124] Participants will be paid $30 for each qualitative interview. In addition, all PNers will also complete semi-structured interviews to gain an understanding of the PN process from their perspective in order to compare and contrast it with the views of the participants themselves. PNers will not be paid for their qualitative interview as they will be conducted during working hours.

9.c. Semi-Structured Interviews: The semi-structured interviews conducted with patients at 1-month post-release and 3-months post release will focus on the Participant/PNer relationship, including: perceived emotional support and rapport, active listening and mutual respect, the presence of direct problem solving and resource linkage, and the amount of contact between the Patient and the PNer. Patient-specific issues, such as reasons for beginning IM in jail and motivation for continuing MM upon discharge, will also be examined. If the participant has dropped out of treatment, transitioned to another MMP or treatment program (e.g., buprenorphine), or failed to engage in treatment upon release from jail, the reasons for doing so will be explored. Women's versus men's experiences with the PN process will be of particular focus. In addition, the PNers will be interviewed during Year 2 of the study in order to gain a broader perspective of the PN process with this population and the factors that have hindered or helped them successfully engage with the patients.

9.d. Qualitative Data Analysis: Semi-structured qualitative interviews will be recorded, professionally transcribed, and analyzed using a grounded theory approach with Atlas.ti qualitative analysis software. Grounded theory is a systematic, inductive approach to the analysis of qualitative data that uses the data itself to generate underlying theories of the key phenomena under investigation. It entails an iterative coding process in which themes, concepts, and ideas within a narrative are continually identified, categorized, questioned, and revised. Two independent coders will analyze the data separately, meet to discuss their findings and coding schemas, and reconcile differences until consensus is reached. We have used this approach extensively in our previous research[80-82,84] and this rigorous strategy will be applied to the current study.

Project Timeline.

Months 1-5 of this proposed four-year project will be devoted to start-up activities, including confirming logistic arrangements, completing the PN manual with consultant Sorensen, training staff, developing detailed procedures with MMP in the Detention Center and the community, obtaining OHRP approval, and finalizing the standard operating procedures.

Participant recruitment and delivery of interventions will begin in Month 6. Approximately four participants (2 male and 2 female) will be enrolled during each week in Months 6-28 yielding a total of 300 participants (100 participants per treatment condition). Follow-up assessments at 1-, 3-, 6-, and 12-months post-baseline will begin in study month 9, and end in study month 42. Although manuscript preparation will be ongoing throughout the study's data collection phase, the last five months of the project, Months 41-48, will be devoted to conducting the final follow-up interviews, data cleaning, obtaining the participant treatment and public safety records, and final outcome analyses and related manuscript preparation.

Dissemination Plan

We will continue to publish our findings in the scientific literature and to make presentations at recognized national and international meetings (see **Progress Report**, above). Locally, we will keep the Baltimore Behavioral Health Systems, the Baltimore City Health Department, the Baltimore-area MMP directors, and the Director of Maryland's Alcohol and Drug Abuse Administration and Department of Health and Mental Hygiene, and the Secretary of the Maryland Department of Public Safety and Correctional Services, up-to-date regarding the study and its implications. At the national level, we will work closely with CSAT's National Addiction Technology Transfer Centers, CSAT's Division of Pharmacologic Therapies to ensure dissemination of the study's progress and findings. The findings will also be shared with the National Association of State Alcohol and Drug Abuse Directors and the American Association for the Treatment of Opioid Dependence to make certain that the state substance abuse agencies and the nation's methadone providers are informed about the study, should it prove effective. Finally, the investigators will work closely with NIDA Notes staff in order to communicate findings to the field.

HUMAN SUBJECTS

Study Participants

There will be 300 adult (150 men and 150 women) study participants. Participants will be recruited from among the opioid-dependent detainees in the Baltimore City Detention Center who are currently receiving opioid detoxification following their arrest. Thirty-six of these participants will also complete semi-structured qualitative interviews at 1- and 3-months post-jail release (see **Process Evaluation**).

Eligibility criteria are: (1) Meets DSM-V criteria for opioid dependence (2) detained for at least 48 hours; (3) receiving opioid withdrawal treatment (as-usual) through the Detention Center's medical providers; (4) able and willing to provide informed consent in English; (5) detained for a charge that, if found guilty will likely not result in a sentence exceeding 1 year; (6) plan to reside in Baltimore upon release.

Exclusion criteria are: (1) enrolled in methadone maintenance (MM) or buprenorphine treatment in the community at the time of arrest; (2) having a medical (liver failure, congestive heart failure) or psychiatric condition (e.g., suicidal ideation, psychosis) that would make participation unsafe in the judgment of the medical staff or PI; (3) pregnancy; (4) allergy to methadone; and, (5) requiring treatment for alcohol or sedative hypnotic withdrawal (i.e., in response to moderate or severe withdrawal).

Patient navigators will provide informed consent and complete semi-structured interviews during Year 2 of the study to examine successes and barriers to entering and remaining in MM treatment across their participant population.

The following material applies to the 300 opioid-dependent detainee participants, and not the two patient navigators, except as otherwise noted.

Research Information

Consenting opioid-dependent detainee participants will be interviewed four times, at study entry during detention (baseline) and at 1,3, 6, and 12 months post-release while in the community. Participants will receive $30 for each of the three assessments in the community for a possible total of $120. No payment will be provided for the baseline interview in the detention center because this could be considered coercive given the financial constraints of incarcerated individuals. However, participants who are re-incarcerated may participate in follow-up interviews, in which case, they will have the option of receiving their $30 payment deposited in their jail or prison account or to have it mailed to a person of their choice. The 32 participants who participate in the qualitative interviews will receive an additional $30 per each of two interviews for a potential total of an additional $60. Follow-up qualitative interviews will not be conducted for re-incarcerated participants because it will not be possible to bring a recorder into the correctional institutions. In addition, participants providing a signed informed consent addendum will be interviewed at 24-months following enrollment and receive $40 for completing that interview.

The patient navigators will not receive payment for their interview because they will be interviewed during regular working hours.

The following instruments will be used to obtain information from the 300 opioid-dependent participants:

Addiction Severity Index (ASI): assesses patient functioning through a 30 -45 minute interview covering 7 key domains over the past 30 days including drug and alcohol use, legal, medical, psychiatric and employment status, family functioning and social relations.[106]

Urine *Drug Testing*: Urine samples will be collected by project staff at 3 and 12 months post-baseline and tested by an approved rapid drug test cup for opiates, methadone, buprenorphine, cocaine, and benzodiazepines. These results will be used for research purposes only and will not be shared with clinic staff.

Modified World Mental Health Composite International Diagnostic Interview (CIDI) for Drug Use Disorders. The updated version of the CIDI-2[107] (termed the World Mental Health CIDI [www.hcp.med.harvard.edu/wmhcidi/index.php]) will be used to determine whether individuals met the DSM-V criteria for opioid and cocaine dependence or remission during the one month period prior to the 3, 6, and 12-month assessments. The CIDI-2 was recommended by an expert panel of the NIDA CTN for gauging DSM-IV remission in clinical studies.[108] It has been shown to have excellent reliability in diagnosing individuals with drug dependence.[109] Its items can be used to determine DSM-5 criteria for substance use disorders.

Arrest and Incarcerations: In addition to self-reports, the official arrest and incarceration records will be obtained for 1 year prior and 1 year post-study enrollment from the Maryland Department of Public Safety and Correctional Services. These records can be used to gauge the severity of offenses, which may change even when arrest frequency remains about the same.

Risk Assessment Battery (RAB): The RAB is a brief questionnaire composed of 45 questions covering substance use and sexual HIV risk behaviors that has been extensively used with drug-dependent populations.[13] The scale's drug-use risk and sex risk scores will be used as outcome measures.

Overdose AE Form. This brief 12 item questionnaire was devised for the present study to examine the number and characteristics and responses to any non-lethal overdoses between study visits.

Methadone Treatment Exposure Questionnaire. This brief 7 item questionnaire was devised for the present study to examine methadone treatment status, anticipated length of sojourn in methadone treatment, and reasons for leaving treatment (if applicable).

World Health Organization Quality of Life (WHOQOL-BREF) is a brief 32-item instrument developed by the World Health Organization that has been used in a wide variety of populations internationally (Noerholm et al., 2004[109d]; WHOQOL GROUP, 1998[109d]; World Health Organization, 2004[109e]) and has been found to have strong psychometric properties (O'Carroll et al., 2000[109f]; Skevington et al., 2004[109g]). The WHOQOL-BREF produces scores in four QoL domains: physical, psychological, social, and environmental. The WHOQOL-BREF also contains a single item, which is not incorporated into any of the four scale scores, asking participants to rate their overall QoL on a 5-point scale from very poor to very good.

Methadone Dose: Methadone dose will be recorded at release from the Detention Center and at each follow-up to permit an examination of the relationship between methadone dose and outcomes by treatment Conditions.

Economic Form 90: The Economic Form 90 survey has been modified for our ongoing research in MMPs and used successfully to collect data on participant outcomes and economic outcomes before, during, and after treatment. This instrument is useful to supplement the ASI whose time frame for follow-up interviews is restricted to the past 30 days for items such as arrest and hospitalization. The Economic Form 90 is a modified version of the Form 90 family of instruments that was originally designed to collect alcohol use and economic outcome data for alcohol treatment studies.112,113 It will be used to collect data on residential drug treatment, outpatient, and emergency room health care utilization; criminal behavior including number of arrests, severity of offense, and nights incarcerated. Also collected will be labor market information including employment status, current wage, frequency of work, and amount of money received beyond paid employment (e.g., Social Security) and off-the-books earnings.

Participant Recruitment

During the first days of opioid withdrawal treatment medical staff providing opioid detoxification will inform patients about the present study and invite them to speak with the research assistant (RA) if they wish to hear about the study. The RA, who will be onsite at the Detention Center up to 5 days per week, will speak with interested inmates in a private room to describe the study to assess interest and to screen for eligibility. The RA will spend about 2 days in the Men's and 2 days in the Women's Detention Center per week and will, if necessary, spend the remaining day at the Detention Center that did not recruit the target number of participants.

Individuals who screen eligible will be asked to sign informed consent that will include permission at the conclusion of the 12 month follow-up period to obtain the participants' official arrest records. The consent will describe the risks and benefits of participation and will include information about alternative treatment options for those not interested in participating. Alternative options that are available at the detention center include completing the non-opioid detoxification as usually prescribed by the medical staff (see **Section 4.1. opioid detoxification)**, and upon release, entering any of several drug abuse treatment programs in the community (if they chose to do so). Individuals refusing participation will be provided with the contact information for the Baltimore Behavioral Health Systems substance abuse assessment and referral line. A consent quiz will be administered to potential study participants up to three times until a score of 100% is achieved. Potential participants who are unable to score 100% on the quiz will not be eligible for participation. For logistical reasons, once a target of about 3 men and 3 women have consented and entered the study in any given week, no more participants will be enrolled that week.

The informed consent process and document will indicate that all participants will receive: (1) information on how to access drug abuse treatment in the community through the Baltimore Behavioral Health Systems centralized phone intake number; (2) substance abuse and overdose prevention information. All participants will be told that they will not receive routine drug abuse counseling while incarcerated but they are able to access mental health services for serious problems including depression and suicidal ideation. They will be told that their decision to accept or reject participation in the study will have no effect on their standing in the Detention Center or have any effect on services that they receive, other than those provided through the study, either during or following detention; that they may choose to withdraw from the study at any time without

jeopardizing their relationship with the criminal justice system or their eligibility for drug abuse treatment services (other than those provided through their participation in the study) in the community.

Participants will also be informed that after completion a series of questionnaires, they will be randomly assigned to one of three study conditions. If they are assigned to methadone detoxification (enhanced treatment-as-usual; ETAU), they will begin a brief detoxification with methadone over several days. If they are assigned to interim methadone, they will receive methadone during their stay at the detention center and will be able to enter one of the four participating methadone programs upon their release from the detention center if they appear at the program within 3 days of release. They will be informed of the potential risks associated with methadone treatment (as described below). Participants will be told that if they are in the ETAU (detoxification) condition, or if they are in the interim methadone condition and discontinue methadone while incarcerated or after release, they may have a greater chance of opioid overdose upon release if they resume opioid use in the community. For this reason, they will be encouraged to enter drug treatment in the community and provided with overdose prevention information. If they are assigned to one of the two Interim Methadone conditions they will be treated with methadone during their stay in the detention center and they will have a guaranteed admission at one of four participating Baltimore City methadone programs upon release, as long as they go to the program within 3 days of release. They will also be told that should they require discontinuation of methadone due to unwanted side effects, because of sentencing or transfer to another facility, rule infractions (e.g., attempted diversion of methadone), or simply a request to discontinue, whenever possible, the participant will undergo a gradual dose reduction under medical supervision and/or using other medications as needed.

They will be informed that if they are assigned to the interim methadone + patient navigator condition, a study staff member serving as patient navigator will meet with them in the detention center to assess potential barriers to their entry into methadone treatment upon release. They will be told that the navigator will be available to them for three months after release to help them enter and remain in treatment. These services may include help: getting a bus pass, arranging childcare, and referring their significant others to drug abuse treatment. Navigators will also be available to provide advocacy for them with their drug treatment program.

Participants will be informed that they will receive a series of assessments at study entry and at 1, 3, 6, and 12 months post-release. A urine sample will be collected during the assessments in the community. They will be told that all of their urine test data and responses to the assessment questions will be confidential and will not effect their treatment at the detention center or in the community. The limits of confidentiality will be explained including threats of harm to self or others, child or elder abuse, or certain communicable diseases (e.g., tuberculosis). They will be informed that their study involvement requires their consent for the research staff to obtain their methadone treatment data from his/her detention center methadone program record, treatment information from the methadone program in the community that they attend as well as admission, discharge dates from any other public drug treatment programs attended during the course of the study, and their arrest and incarceration records from the criminal justice system.

In addition, participants who provide a signed informed consent addendum will be interviewed at 24-months after enrollment using the same interview and urine collection approach as for the 12-month interview.

Potential risks

Risks of substance abuse. Risks of opioid and/or other substance abuse include: overdose death, infections including but not limited to endocarditis, soft tissue infection, hepatitis, kidney infection, HIV infection, seizure, stroke, and trauma from motor vehicle, machinery, or violence.

Risks of methadone treatment. The use of methadone in this study poses no additional risk than that of methadone provided under routine treatment conditions in the methadone clinics in the detention center and in the community. When taken under medical supervision, methadone is a generally safe and effective treatment for opioid detoxification and maintenance. The major risk of methadone treatment (as with heroin and other opioids) is over-sedation which can lead to respiratory depression and death from overdose. This can very rarely occur during the initial phase to methadone dose induction. Participants assigned to detoxification will be treated with low doses of methadone and will be carefully monitored by nursing staff on a daily basis making this risk very unlikely. Participants in interim methadone treatment will begin treatment with a low dose which will be slowly increased. They too will be monitored by nursing on a daily basis, making this risk unlikely as well. Interim methadone treatment has been found to be as effective as methadone with counseling early in the first four months of methadone treatment in community-based settings where there is even more opportunity to use illicit drugs than during incarceration. Therefore, interim methadone should not

pose any additional risks than standard methadone treatment. All participants will be informed of the availability to all detainees of mental health counseling for depression and suicidal ideation while incarcerated should they need it.

Potential participants will be told that the most often reported side effects of methadone (some of which are associated with receiving too low or too high a dose) are trouble sleeping, nervousness, drowsiness, dizziness, vomiting, sweating and constipation. Operating an automobile or machinery may pose risk if the participant becomes drowsy. Other side effects may include palpitations and fainting which could be a sign of an irregular heart beat, which could in very rare instances lead to sudden death. Other individuals may experience trouble urinating, decreased sexual desire or potency, or allergies (including itching, rashes and swelling). Stopping methadone treatment suddenly will lead to opiate withdrawal symptoms. Finally, if the participant becomes pregnant during methadone treatment, they should seek obstetrical care.

Emotional discomfort. There is a small chance that participants may become upset when discussing their history of drug use or sexual behavior or responding to any of the self-report measures or interview questionnaires. We will discontinue administration of research instruments if a participant shows discomfort. If necessary, the PI or Co-I Dr. Jaffe, both psychiatrists, or medical staff from the Detention Center will meet with the participant to alleviate any problems.

Confidentiality. Participants will be asked to provide information regarding a number of sensitive behaviors (e.g., drug use, sexual behaviors, and illicit activities). The inappropriate release of such confidential information could result in loss of employment, arrest, or social problems. Careful steps to minimize such risks will be taken as described below.

Protection Against Risks

Risks Associated with Substance Abuse. The above-mentioned risks of continued substance use are considered symptoms of the participants' underlying substance use disorder and serious adverse events related to these risks are to be considered expected. Efforts to minimize these risks include providing at a minimum enhanced treatment as usual (ETAU) in all three study conditions which includes providing drug abuse information, overdose prevention information, and a referral to community harm minimization (needle exchange and overdose prevention) as well drug abuse treatment programs.

Risks Associated with Methadone Treatment. Every effort will be taken to minimize the likelihood of risks to participants that are associated with the known side effects of methadone as described in its FDA-approved label. Any known side effects of methadone treatment will be considered expected adverse events.

In an attempt to reduce potential risks associated with methadone treatment, participants receiving methadone (detoxification or interim) treatment will be carefully monitored by trained nursing and medical staff who are working in accredited methadone treatment program. Methadone program staff provide patient education on methadone and its side effects. A slow dose induction process, including daily observation by nursing will minimize the likelihood of oversedation and overdose death during the dose induction process. Methadone treatment in the community will be standard care and its risks will not differ from those routinely offered to patients in the US.

Participants who will be informed that if they are assigned to detoxification or if they are assigned to interim methadone and discontinue treatment in the Detention Center or after release, they are at relatively increased risk of overdose death if they resume opioid use. This is the same risk they would face if they did not enter the study and were detoxified with non-opioid medications in the Detention Center. They will be provided with overdose prevention information, and encouraged to attend drug abuse treatment in the community.

Participants will be told of the importance of informing their physicians in the Detention Center and in the community of all the medications they are taking (including methadone) and to inform their physicians if they experience any of side effects of methadone. They will also be informed of the risk of overdose death and other medical problems described above of using alcohol and/or other prescription or illicit drugs with methadone including benzodiazepines, phenergan, and clonidine.

Participants receiving interim methadone in the Detention Center who request or require discontinuation of methadone due to unwanted side effects, sentencing or transfer to another facility (e.g., for behavioral reasons or sentencing), rule infractions (e.g., attempted diversion of methadone), or simply a request to discontinue, whenever possible, will receive a gradual dose reduction under medical supervision and/or treatment with other medications.

Confidentiality. We have obtained a Federal Certificate of Confidentiality to protect against the release of confidential information; we will provide all staff with training on their responsibilities for maintaining participant confidentiality; we will use unique identifiers to identify subjects in the database; all data will be kept in locked filing cabinets to which only the investigators and project manager will have access. Encrypted data will be transmitted electronically via the web to a secure server to the University of California at Los Angeles Data Management Unit which has double password protection on its server and files. All data transmitted in over the web are de-identified. Identifying information will be removed from all study data prior to publication or presentation. Quantitative data will be aggregated to further protect the confidentiality of participants.

Risk/Benefit Ratio

Every effort will be made to minimize the risks to participants in this study. Exclusion criteria, (e.g., medical status), voluntary participation, and careful medical monitoring and protection of confidentiality will help minimize risk to subjects. With regard to study benefits, all participants will receive better drug abuse treatment than afforded to detainees who chose not to enroll in the study. All participants will receive specific drug treatment referral information for community-based treatment as well as overdose prevention information. Participants in the methadone detoxification condition will receive methadone rather than clonidine and other non-opioids for detoxification (as is provided to non-study participants) which will afford them a more comfortable detoxification experience. Participants in the interim methadone condition will receive methadone during their stay in the Detention Center with the opportunity to continue in the community, and those in the patient navigator condition will receive extra assistance in gaining entry and remaining in treatment.

Results from this study may help determine the benefits of interim methadone with or without patient navigation compared to a medically appropriate detoxification and thereby may inform policy makers about effective and cost-effective treatments that could be implemented more widely.

Importance of the Knowledge to be Gained

There is only one jail-based methadone program in the US (in New York) that we are aware of that *initiates* methadone treatment routinely for detainees. The proposed study will address several barriers to implementing such programs. It may provide policy makers with effectiveness and cost-effectiveness data on interim methadone in jails which may convince them of the benefits of providing methadone in jails. It will show the effectiveness of methadone without counseling in jails, which will help to overcome the lack of funding for counselors, one of the significant barriers to providing methadone treatment in jail. Finally, by pairing patient navigator with interim methadone treatment, the proposed study will examine a promising approach to overcoming the relatively low rates of entry into treatment following release and shorter stays for those who do enter.[20,22]

Participation of Prisoners

The proposed study involves research on prisoners and therefore is subject to DHHS regulations that provide additional protections for research involving prisoners as research participants. In keeping with their vulnerable status as prisoners, all study participants will receive an intervention that is superior to their treatment as usual, including methadone detoxification or interim methadone while incarcerated, overdose prevention information, and drug abuse treatment referral information.

We are sensitive to the possibility that, given the limited financial resources of many prisoners at this point in time, providing cash compensation at baseline could unduly influence prisoners to participate in this intervention study. Furthermore, we consider that the treatment that participants receive is ample compensation for the time that they devote to research procedures at baseline. Therefore, no cash compensation will be provided for baseline assessments. Cash compensation will be provided for follow-up interviews conducted following release in recognition of participants' contribution of their time and efforts to the research.

We have obtained WIRB's approval for the study. WIRB has a prisoner advocate and is quite experienced in reviewing prison research.. We have also received approval of the protocol from the Maryland Department of Public Safety and Correctional Services Research Review Committee. The FRI IRB has obtained approval for the study from the Federal Office of Human Research Protection.

Data and Safety Monitoring Plan

Responsibility for Safety Oversight

The Principal Investigator and his study staff (including the project's statistician), the Western Institutional Review Board (WIRB), and a Data Safety Monitoring Board (DSMB) from UCLA will provide safety oversight for the project. The PI will be responsible for conducting a literature search on methadone treatment in jails and prisons no less frequently than every six months to identify any emerging research findings that might influence study procedures. Finally, the PI will remain alert to any changes in the FDA labeling of methadone.

Report of Safety-Relevant Information to NIDA

The Principal Investigator is responsible for informing NIDA of any safety-relevant actions taken by WIRB as a result of its regular annual reviews and any special reviews of this project. In addition, the PI will inform NIDA of any major changes in the protocol or its status including: protocol amendments; procedural changes; suspension or termination of subject accrual or of the protocol itself; changes in the informed consent or IRB approval status; and other problems or issues that could have a significant impact on individuals' consent to participants. The PI will provide the minutes of the DSMB meetings to NIDA.

Serious Adverse Event Reporting

Serious adverse events (SAE's) include any of the following outcomes for the participant: 1) death; 2) acute life-threatening incidents; 3) hospitalization or the prolongation of a hospitalization; 4) persistent or significant disability or incapacity; or, 5) birth defects. Should they occur, these events may be communicated to the PI by participants and/or staff, or may be observed directly by the PI. SAE's will be reported to the UCLA DSMB and NIDA regardless of whether they are considered study related.

In any given case, the PI will make an initial SAE report to the DSMB and the study's medical safety monitor within 48 hours. SAEs that are unexpected and definitely or probably study related will also be reported to the DSMB within 48 hours. The PI will submit follow-up reports on participants who have experienced an SAE until the outcome of the event is known. This follow-up information will be reported to the DSMB and NIDA staff. A summary of SAEs will be reported to NIDA Program staff through the annual non-competing renewal application mechanism.

Reporting of Unanticipated Risks or New Findings

The PI will report any information related to unanticipated risks or new information that may change the risk-benefit ratio to WIRB and DSMB, and the NIDA Program Official. This information may consist of findings from the current study or other studies. Any changes in the protocol or informed consent as a result of this information will be promptly reported to the NIDA Program Official.

The PI will also report any irregularities in the conduct of the study such as improper participant enrollment, obtaining of informed consent, and data collection or processing to WIRB and DSMB, and the NIDA Program Official. The PI will report to WIRB Promptly Reportable Information according to its guidelines. This reportable information includes: an audit, inspection or inquiry by a federal agency, written report from a federal agency, State medical board action, allegation of noncompliance or finding of noncompliance, suspension or premature termination by the sponsor, investigator, or institution; new or increased risk; adverse events that require a change to the protocol or consent; protocol deviation that harmed a subject or placed subject at risk of harm; protocol deviation made without prior IRB approval to eliminate an immediate hazard to a subject; breach of confidentiality; Unresolved subject complaint; or Other information the sponsor/CRO/other has directed the PI to report to the IRB, even if not on this list and does not meet any of the reporting requirements.

Performance Monitoring

The PI will review of study activity with regard to:

- informed consent process;
- fidelity to inclusion and exclusion criteria;
- SAE reporting.

Problems found during performance monitoring will lead to a corrective action plan, which will be subsequently monitored for implementation.

Quality Control of Data

Interviewers will be thoroughly trained regarding administration of interviews and completion of forms and their work will be reviewed on an ongoing basis. Interviewers will review case report forms (CRF's) for completeness and accuracy. The Project Manager will review CRF's the next day through the QA checks in the web-based data entry system. The Project Manager will advise the interviewers of any forms needing

correction. Prior to the conduct of inferential analysis, the raw data will undergo extensive examination for completeness and accuracy by the data entry staff, under direction of the project's statistician.

Data and Safety Monitoring Board (DSMB)

As in all of FRIs randomized clinical trials including our studies of interim methadone and methadone treatment in prison, a DSMB of outside experts in clinical trials and biostatistics will be created to review the progress of the study and monitor participant intake, outcomes, SAEs, and other safety related matters. The DSMB will meet at the start of study enrollment and every six months for the first year of enrollment and annually thereafter. Members will include a physician expert in the opioid agonist maintenance treatment of heroin dependence and a statistician. The DSMB will review all SAEs. The project's statistician will perform interim analyses, if so requested by the DSMB, to determine whether the study should be terminated early as a result of preliminary findings. The Board will also review study enrollment and feasibility as well as the nature and frequency of SAEs in reviewing the safety of the study. DSMB meetings will be convened as needed to discuss new findings, unexpected SAEs that are considered related (or probably related) to the interventions under study, or results of any other new findings in the literature that pertain to this study. All DSMB reports will be sent to the PI who will forward copies to the IRB and to NIDA.

Criteria for Suspending or Terminating the Study

The study may be modified, suspended, or terminated at the recommendation of the PI, DSMB, or by WIRB in the interests of protecting study participants. The study will be modified to comply with any FDA-approved labeling changes for methadone administration. The PI, DSMB, or IRB may recommend modifying, suspending, or terminating the study based on the SAE reports. Trials may be terminated for any one or more of four classes of reasons as determined by the DSMB, as specified below: 1) safety/adverse events; 2) favorable benefit-risk ratio; 3) unfavorable benefit-risk ratio; and 4) inability to answer questions regarding trial efficacy.

Termination Due to Safety/Adverse Events:

The DSMB's recommendation to stop the study with regard to safety/adverse event considerations will be based on the number and severity of unexpected, study-related SAEs.

Termination Due to Favorable Benefit-Risk Ratio:

If the DSMB determines that an interim analysis is required and such an analysis provides compelling evidence for the efficacy of the experimental intervention(s), early termination may be recommended. Such a recommendation would not be made without consideration of other relevant information related to the trial and an assessment of the strength of evidence of benefit.

Termination Due to Unfavorable Benefit-Risk Ratio:

If the interim efficacy analysis results show compelling evidence for a lack of clinically relevant outcomes, early termination may be recommended by the DSMB. Such a recommendation would not be made without consideration of other relevant information related to the trial (e.g., safety/adverse event issues).

Termination Due to Inability to Answer Trial Question:

If there are serious flaws in the data or the implementation of the study, the DSMB may recommend termination because the questions concerning efficacy are unable to be adequately addressed. These problems include serious problems in the recruitment/enrollment of participants; threats to internal validity, external validity, construct validity, and/ or statistical conclusion validity. As with the other types of reasons for study termination, noted above, the DSMB will make this recommendation in consideration with other relevant information regarding the trial.

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