Friends Research Institute

Health Services Research:
Extended Release Naltrexone for Opioid-Dependent Youth

Protocol

Version 14.0

March 11, 2016

Revision Dates:	Version #	Summary of Changes
3/2/2016	14.0	1. Participant liver function will be assessed at months 1 and 6 if the participant receive XR-naltrexone in the previous month to provide additional safety data.
11/13/2015	13.0	1. The study team will follow any study participant who becomes pregnant during their study participation in order to collect pregnancy outcome information. In the event of such pregnancy the woman should consult with her doctor to determine whether or not to discontinue use of XR-NTX.
8/18/2015	12.0	1. Modification noting the Certificate of Confidentiality has been obtained. 2. Modifications concerning the qualitative sample size and parental/caregiver sample inclusion for the qualitative sub-sample.
11/5/2014	11.0	1. Add the option to conduct consent/re-consent adult participants telephonically.
9/8/2014	10.0	1. Refine admission lab review to remove 3 day specification 2. Add contingency management reinforcement for follow-up visits attended in-person
5/23/2014	9.0	3. Remove eligibility requirement of approaching within 3 days of admission 4. Two additional AE follow-up months will be conducted for any participant, who receives a XR-NTX injection at month 6 5. New data Collection forms: 1) Treatment Preference; 2) Discharge Treatment Received; 3) Doctor's Questionnaire - Patient Course of Treatment; and 4) Patient Course of Treatment Questionnaire
1/29/2014	8.0	1. Expand psychosocial treatment offered by MMTC or a facility the participant selects.
1/16/2014	7.0	2. Expand inclusion criterion #2 to include those who report receiving treatment for opioid withdrawal elsewhere prior to direct transfer to MMTC.
12/12/2013	6.0	3. Participants who fail to receive their allocated intervention will be followed throughout the study.
11/22/2013	5.0	1. Modified the seven days window without Buprenorphine or other opioids prior to beginning the Naltrexone challenge to allow a minimum six day window when necessary. 2. Baseline urine drug testing will not include methadone; however methadone will be tested prior to xr-ntx induction and monthly thereafter as necessary based on randomized condition assignment.
9/26/2013	4.0	1. Clarified participant payments 2. Observation of withdrawal symptoms during Naltrexone Challenge reduced to 2 hours rather than 4 hours. 3. The consent and assent forms, protocol, and human subjects section were modified to present an alternative 2-day naltrexone challenge option, as some patients are unable to remain inpatient for the full 3 days. 4. Depression is assessed and liver function tests (ALT and AST), as well as a urine pregnancy test for female participants will be administered prior to treatment admission. The 21-item BDI, which has been used extensively, including among youth,95-98 will be administered as a baseline assessment and repeated monthly at the same time as urine collection for drug testing to screen for depression and suicidal ideation. 5. The abbreviated RAB will be administered rather than the 45 questions. 6. Depression was added as one of the reporting adverse event items. This aligns with the DSMP. 7. Added DSMB and FDA to the AE summary report recipients. This aligns with the DSMP.
8/9/2013	3.0	1. The protocol was modified to include the use of DSM-5 instead of DSM-4 criteria. 2. The protocol and human subjects sections were modified to clarify the process by which physiological dependence on benzodiazepines is assessed as part of the clinical treatment process. 3. The protocol was modified to remove OraQuick HIV Testing and replace HIV testing with blood draw. 4. The protocol was modified to include the full range of alternative treatment options for patients who opt not to participate in the study.

Revision Dates:	Version #	Summary of Changes
		5. The consent and assent forms were corrected to accurately reflect the induction process by removing the description of the Narcan challenge. 6. The description of the pre-screening process was modified to incorporate a review of MMTC records in lieu of administering the CIDI-2 for benzodiazepine dependence. 7. The World Health Organization Quality of Life – BREF (WHOQOL-BREF) was added as a supplemental measure. 8. The protocol and consent forms were modified in order to clarify that only participants assigned to XR-NTX who receive their final medication injection at month six will be interviewed at month 7 and month 8 to be queried about adverse events.
6/26/2013	2.0	1. Expansion of the study population to include participants 15 and 16 years of age. 2. Changing the information in the consent/assent forms, protocol, human subjects sections and recruitment flyer regarding depression and suicidal ideation so that it is more consistent with the FDA approved label of Vivitrol, including risk of suicidality. 3. Modifying the consent/assent forms so they are consistent with the protocol regarding the medication induction process. 4. Adding two additional exclusion criteria to the protocol: body mass index > 40 and blood coagulation disorder. 5. Deleted mention in the consent/assent forms of XR-naltrexone being provided by Alkermes. 6. Adding language to the consent/assent forms to indicate that XR-naltrexone may block the effects of cough medication containing codeine or medications to treat diarrhea that contain opioids and that the safety and effectiveness of XR-naltrexone has not been proven in a pediatric population. 7. Updating the flier to make the eligibility criteria more consistent with the protocol and to indicate that there are other potential risks that can be explained to those interested in hearing more about the study. 8. Updating the protocol's description of the screening procedures, as well as the data collection schedule, to include medical history and physical, and have updated Figure 1 to include all laboratory tests conducted throughout the study. 9. Updating the screening procedures to include screening for coagulopathy during history of physical exam. 10. Updating the protocol and human subjects section to indicate that subjects and their parents will be instructed to contact medical staff at the study site through its 24-hour number, as needed, for any medication-related concerns. 11. Modifying the protocol and human subjects section to increase LFT monitoring of subjects receiving XR-naltrexone as follows: baseline, and at the 1 month, 3 month, and 6 month XR-naltrexone injections. 12. Modifying the protocol as well as the human subjects section to indicate that urine pregnancy tests will be conducted monthly on all females. 13. Modifying the protocol and the human subjects section to indicate that an Adverse Event (AE) follow-up report will be obtained at 4 weeks and 8 weeks following the 6 month dose of XR-naltrexone. 14. Modifying the exclusion criteria and the human subjects
3/27/2013	1.0	FDA Approved protocol

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1. SPECIFIC AIMS

Heroin and illicit prescription opioid use and dependence among youth are serious public health problems that have grown at an alarming rate in the past decade.[1-3] Opioid use and dependence are accompanied by adverse health and legal problems, including risk of overdose death, HIV and hepatitis infection, criminal behavior, and arrest.[4-6] Despite the availability of pharmacotherapy, including, most recently, extended-release naltrexone (XR-NTX), medications are infrequently used to treat opioid-dependent youth. Treatment-as-usual (TAU) for this population consists for the most part of detoxification (on an inpatient or outpatient basis) followed by drug-free counseling or, to a lesser extent, longer-term treatment with buprenorphine.[6,7] Despite calls to increase the study of pharmacotherapy for opioid-dependent youth,[8,9] to date there have been only two short-term clinical trials with buprenorphine.[7,10] No studies have examined XR-NTX with opioid-dependent youth.

Extended-release naltrexone (XR-NTX), developed to overcome the adherence challenges associated with oral naltrexone,[11] has recently been approved by the US FDA for the prevention of relapse to opioid dependence. XR-NTX is not approved for pediatric use and the FDA approved labeling for Vivitrol does not indicate a lower age range for its use. However, the FDA considers 17 year olds and above to be adults. Nevertheless, very few participants 18 through 21 years of age have been included in previous adult XR-NTX trials, and no clinical trials have addressed the use of XR-NTX specifically for 15 to 17 year olds. The pivotal trial for approval of XR-NTX, conducted in Russia, had a mean sample age of 29.5 years (SD=4.2) and found that adults randomly assigned to receive monthly injections of XR-NTX, compared to placebo injections for 6 months, had significantly higher rates of confirmed abstinence.[12] The availability of XR-NTX offers promise as an alternative treatment for opioid-dependent youth but there are limited data on its use in this population and no comparative effectiveness data of the extent to which it yields treatment outcomes superior to TAU.

The present proposal describes a 6-month two-group comparative effectiveness trial of XR-NTX v. TAU for 340 opioid-dependent youth ages 15-21. The proposed study will be conducted at Mountain Manor Treatment Center (MMTC), a highly experienced community-based adolescent drug abuse treatment center that has conducted research with both XR-NTX and buprenorphine for opioid-dependent youth.[7,13] The study team has considerable experience using XR-NTX among adults[14] and has published the only report to-date on the use of XR-NTX in youth.[13] TAU will consist of the typical treatment approach provided to opioid-dependent youth in the US, namely initiation of buprenorphine for the treatment of opioid withdrawal followed by counseling with or without continued buprenorphine in the community.[7,13]

The **Specific Aims** are:

Aim 1: To determine the relative effectiveness of XR-NTX compared to TAU for opioid-dependent youth in terms of the following 3- and 6-month outcomes: a) days in treatment; b) opioid use; c) other drug (cocaine and marijuana) and alcohol use; d) criminal behavior and arrests; e) relapse to DSM-5 defined opioid use disorder.

Aim 2: To examine the impact of XR-NTX on HIV drug- and sex-risk behaviors at 3- and 6-month follow-up and HIV infection status at 6 months.

Aim 3: To evaluate the cost, cost-effectiveness, and cost-benefit of XR-NTX *v.* TAU among opioid-dependent youth.

This application is of high public health significance because of the growth of opioid use and dependence among youth and their association with overdose death, HIV and hepatitis infection, criminal behavior, and arrest. There is a significant gap in empirical knowledge regarding the use of pharmacotherapy for opioid-dependent youth,[6,8-10,13] a gap that is acutely evident by the paucity of published literature on XR-NTX treatment for youth. The proposed study is highly innovative because there have been no studies in this population of XR-NTX, no use of DSM-defined opioid use disorder as an outcome measure, and no economic analyses of treatments. Cost data will be of considerable use to policy-makers and treatment program directors in order to optimize treatment resources. The emphasis on examination of treatment outcomes in a community treatment setting approximating "real world" conditions will enhance the likelihood that study findings will be of immediate use to clinicians and practitioners. The proposed project's findings have the potential to impact patients, public health, and public safety by reducing opioid use and its associated problems in this vulnerable population.

2. RESEARCH STRATEGY

2.1. Significance & Background

Opioid Use and Dependence is a Growing Problem among Youth. Opioid use among youth has risen dramatically in the past decade. Nonmedical use of prescription drugs, including opioids, is now the second most frequently used drug among 12-to-17-year-olds, second only to marijuana.[3] Correspondingly, treatment admissions for opioid use disorders among 12-to-20-year-olds increased 196% between 1995 and 2005.[15] Adolescent opioid dependence is associated with numerous negative outcomes, including HIV transmission, overdose death, criminal behavior, and other social problems. Unlike the popular conception of the adult heroin problem as restricted to the disadvantaged inner city, youth opioid dependence, especially prescription opioids, is experienced by a much broader demographic, including suburban and higher socio-economic groups.[16]

HIV Drug- and Sexual-Risk Behaviors are Associated with Opioid Dependence among Youth. Opioid dependence among youth is associated with HIV risk behaviors including drug injection and risky sexual behaviors.[5,17,18] When compared with treatment-seeking adolescents with cannabis and/or alcohol use disorders, youth with opioid use disorders have significantly higher rates of lifetime injection drug use and of unprotected sex in the past 30 days.[18] Meade et al.[5] found that approximately 50% of opioid-dependent youth reported injection drug use risk and 65% reported unprotected sex within the month prior to treatment admission. However, there is very limited scientific knowledge regarding the impact of pharmacotherapy for opioid-dependent youth in reducing HIV risk behaviors.[5,6,10]

Treatment Outcomes for Opioid-Dependent Youth. Our previous research has shown that youth who are dependent on opioids compared to other substances have higher

rates of post-treatment substance use and worse functional outcomes.[19] Despite its relative lack of effectiveness, the community standard of care for opioid-dependent youth remains detoxification (on an inpatient or outpatient basis), followed by drug-free counseling.[6,7] Unfortunately, youth have high rates of leaving treatment "against medical advice" from detoxification, and poor retention in drug-free counseling.[10] As noted in a recent Cochrane Review,[20] there have been very few rigorous studies of addiction pharmacotherapy in youth, all of which were limited to relatively short-term buprenorphine treatment.[7,10,20] Moreover, very few participants 18 through 21 years of age have been included in previous adult XR-NTX trials. Thus, the availability of XR-NTX provides the opportunity for a timely and significant study in this special, high-risk population.

Need for a Broader Perspective on Treatment Outcome. In contrast to most drug abuse studies, when the effectiveness of naltrexone is tested as a treatment for alcohol dependence, outcomes are not limited to abstinence, but also consider the number of non-drinking days and the number of drinking days where use is not excessive.[21] There is evidence from some studies of opioid dependence (e.g., Robins[22] study of returning Viet-Nam veterans) and alcohol dependence in non-treatment-seeking individuals (e.g., Dawson and colleagues[23] NESARC study), that alcohol or drug use among individuals who were once dependent does not necessarily initiate a full-blown relapse to dependence. Therefore, in the present proposal, the examination not only of opioid use but of the DSM-5 defined diagnosis of opioid use disorder will provide a particularly innovative and significantly broader perspective on treatment outcome among youth.

Extended-Release Naltrexone. Oral naltrexone is a μ-receptor antagonist that was FDA-approved in 1984 to treat opioid dependence in the US. It blocks the effects of self-administered heroin and other opioids but, unlike buprenorphine, has no opioid agonist effects. Unfortunately, poor adherence has seriously hampered its effectiveness. Thus, it is infrequently used in clinical practice.[24] Extended release naltrexone (XR-NTX) was developed to address this limitation. It is a long-acting intramuscular injection that is provided monthly and was recently approved by the FDA for the prevention of relapse to opioid dependence.

XR-NTX was approved in the US in 2006 for the treatment of alcohol dependence. It provides sustained therapeutic naltrexone blood levels for approximately 30 days.[25] To date, there has been a safety study of XR-NTX among adult opioid users, a short-term, two-site, placebo-controlled randomized trial with adults in the US,[26] and a 13-site, double-blind, placebo-controlled trial conducted in Russia among adults.[12] In the latter study, following inpatient detoxification, 250 opioid-dependent adults were randomly assigned to monthly, double-blind XR-NTX or placebo injections for 6-months accompanied by outpatient counseling. The median proportion of confirmed weeks of opioid abstinence among participants receiving XR-NTX was 90% over the 6-month trial compared to 35% for placebo ($p < .0002$). Total abstinence during the trial was reported in 35.7% of participants receiving XR-NTX compared to 22.6% on placebo ($p < .03$). Six-month retention in treatment with XR-NTX was 53%, significantly better than placebo ($p< .02$) and comparable to the retention rate found in studies of buprenorphine maintenance with adults.[27]

Extended-Release Naltrexone in Youth. We are not aware of any published clinical trials of XR-NTX treatment in individuals 21 years of age and younger, despite FDA approval for use of XR-NTX in 17-20 year old children. Although 18-20 year-olds were eligible for participation in the pivotal XR-NTX trial in Russia, the reported mean and standard deviation of the age of this sample [M= 29.5 (SD=4.2)] would suggest that there were few participants between 18 and 20 years of age, an age considered "children" by NIH because of their developmental issues distinct from adults. The only published report of XR-NTX in opioid-dependent youth was an open-label study by Co-I Fishman (see Preliminary Studies). Thus, study of XR-NTX in youth 21 and under is of high public health significance and will fill an important gap in scientific knowledge.

Economic Studies of Youth Drug Abuse Treatment. Numerous studies have examined the costs[28-36] and cost-effectiveness or cost-benefit of pharmacological treatments for adults with substance abuse problems, primarily for methadone maintenance treatment[37-44] and more recently buprenorphine.[37,45-49] However, findings for adult programs are not always transferrable to adolescent programs[50] due to factors that may affect adolescents' drug use behavior in different ways such as peer drug use, school failure, family dysfunction, and social development.[50,51] In recent years, specialized treatments, including pharmacological treatment, have been developed to address the unique needs of substance-abusing youths and important studies continue to be conducted to evaluate their effectiveness; yet there are few economic studies of these treatments.[50,52-55] Given the limited resources available for drug abuse treatment, we need to fully understand the costs and benefits associated with such treatment for youth, including newer pharmacological treatments. The scarcity of such economic studies clearly demonstrates the need for additional research in this area to build our knowledge base and improve our understanding of cost-effective treatment options.

Summary of Significance. Opioid dependence in youth is a growing problem in the US that is associated with serious public health consequences, including increased risk for HIV exposure. The present proposal will provide important comparative effectiveness data on the relative impacts of XR-NTX and treatment-as-usual (TAU) on days retained in treatment, opioid and other drug and alcohol use, DSM-5 opioid use disorder, criminal behavior and arrest, and HIV risk behaviors among youth ages 15-21. It will fill a significant gap in scientific knowledge regarding pharmacotherapy in this under-studied population. Given the less-than-ideal outcomes for youth receiving TAU in the US, the present study will have considerable importance for researchers, clinicians, program directors and policy makers, and is very likely to have significant and widespread impact. The cost analyses will provide important data to policymakers and treatment providers.

2.2. Innovation

The proposed study is highly innovative as it would be the first study to examine the effectiveness of XR-NTX with opioid dependent youth, a medication that has been shown to be effective among adults for the treatment of opioid dependence.[12,26] Indeed, as described above (see Extended-Release Naltrexone in Youth), our team has the only published empirical study on XR-NTX in this population. Therefore, the present study will fill a significant gap in scientific knowledge concerning the treatment of opioid-dependent youth. In addition, the use of the DSM-5 diagnosis of opioid use disorder as

an outcome measure, complementary to the traditional outcome of urine testing results, represents a significant and innovative approach. Furthermore, there have been few economic studies of pharmacotherapy with this population, and none involving XR-NTX, thus adding to the proposal's innovation.

Preliminary Studies: Building Towards the Present Proposal

Our research team has extensive experience conducting randomized clinical trials (RCTs) with opioid-dependent adults with buprenorphine, methadone, and XR-NTX, as well as with opioid-dependent youth with buprenorphine. In addition, the team has extensive clinical experience with providing XR-NTX for youth 21 years of age and younger, which is the target population for the present study.

The PI recently completed a NIDA-funded challenge grant that successfully enrolled its targeted sample size of 320 adult participants for a random assignment comparative effectiveness trial to two levels of counseling provided with buprenorphine.[56] She collaborated with Co-I Schwartz on his NIDA-funded study that examined entry and engagement in opioid agonist treatment that led to 13 publications, including mixed methods and qualitative research (see Biosketch). Co-I Schwartz was PI of RCTs of methadone v. waiting list[57,58] and methadone with two levels of counseling.[59,60] He is Co-I on an RCT of buprenorphine for prisoners,[61] and was Co-I on two studies of XR-NTX with Co-I Fishman.[14] Co-I Fishman has extensive experience treating patients and conducting trials with buprenorphine.[7] He serves as site PI for the ongoing NIDA-funded multi-site trial of XR-NTX for probationers (O'Brien, PI). Thus, the team has extensive experience conducting RCTs for the treatment of opioid dependence.

Co-I Fishman is one of the few clinical researchers with experience in the use of XR-NTX for adolescents. He recently published the first report of XR-NTX treatment of opioid-dependent youth in Addiction.[13] The average age of the 16 participants was 17.8 years (range 15-20). Of the 16 youth who received an injection, 12 (75%) received at least a second dose, and 10 (63%) continued in treatment for at least four months. There was substantial reduction in opioid use in 11 participants (69%) at four months. Thus, our preliminary research with XR-NTX and buprenorphine in youth makes a study comparing XR-NTX to TAU the next logical step in our research agenda.

Willingness of Opioid-Dependent Youth to be Randomly Assigned to Medications. Youth have been successfully enrolled in a number of RCTs of drug dependence treatment throughout the US, involving both psychosocial treatment[28] and pharmacotherapy,[10] including RCTs conducted at the study site.[7] In order to determine whether youth would agree to be randomly assigned to XR-NTX or TAU (consisting of varying lengths of buprenorphine treatment), a survey that provided information about XR-NTX and buprenorphine was administered to 102 youth ages 15-20 who were asked whether they would be willing to be randomly assigned to receive one of these medications in the context of a research study. We found that 66% of the pilot study participants reported that they would agree to be randomly assigned within such a study. We have used these data as a basis for our recruitment projections.

2.3. Investigators

Shannon Gwin Mitchell, Ph.D. (PI) is a Research Scientist at Friends Research Institute (FRI) with expertise in research on the treatment of opioid dependence and HIV risk behavior. She is PI of the above-mentioned NIDA-funded challenge grant. Moreover, she has collaborated for the last five years with Co-I Schwartz on two NIDA-funded studies. The first examined entry and engagement in methadone treatment (see Biosketch) and recently received continued funding as a competing continuation. The second is an ongoing RCT of SBIRT in New Mexico. She is also an expert in qualitative research in HIV and addiction treatment and has numerous publications emanating from that work. Finally, she and Co-I Fishman are investigators in the Mid Atlantic Node of the Clinical Trials Network (CTN) that is jointly led by the present study's Co-I Schwartz. Dr. Mitchell's experience as PI and Co-I of RCTs of treatment for opioid dependence, in conducting qualitative research, as well as her longstanding collaboration with Co-I Schwartz and the strong clinical partnership with Co-I Fishman, makes her well-suited to lead the study.

Marc Fishman, M.D. (Co-I) is the Medical Director at the Mountain Manor Treatment Center (MMTC). Dr. Fishman has extensive experience in treating adolescent and young adults and in conducting research with XR-NTX. He participated with Co-I Schwartz in the multi-site pilot study of XR-NTX in adult probationers[14] and is currently study physician and site PI for a NIDA-funded study of XR-NTX for opioid-dependent adult probationers. He has led the group at MMTC in implementing the youth opioid treatment track, using a combination of buprenorphine, XR-NTX, and medication-free treatment[6,62] and has published the only paper, of which we are aware, on XR-NTX clinical experience with youth.[13] Dr. Fishman served as a member of the research team for two CTN pharmacotherapy trials for adolescents at MMTC, including the study of buprenorphine[7] and of Concerta™ for ADHD and substance abuse. He is the site-PI of an ongoing NIDA-sponsored multi-site study of vigabatrin for cocaine dependence. He has also been PI of several CSAT-funded adolescent drug treatment projects (see Biosketch).[19,63-65] Dr. Fishman is also a national leader in disseminating evidence-based practices in pharmacotherapy for addictive disorders among youth. He is well qualified to oversee the clinical services and assist the PI in disseminating research findings.

Robert Schwartz, M.D. (Co-I) has been the Medical Director of FRI for the past 12 years. He has extensive clinical experience in the pharmacotherapy of opioid-dependent patients and has served as PI on four NIDA-funded studies of opioid dependence (including three RCTs). As described above, he has collaborated extensively with both the PI and Co-I. He has served as Co-I on RCTs of buprenorphine[61] and methadone for prisoners[66] as well as XR-NTX for probationers.[14] Dr. Schwartz is well-suited to assist the research team in providing clinical trials oversight and in disseminating findings.

Laura Dunlap, Ph.D. and Gary Zarkin, Ph.D. (Co-Is) have extensive experience conducting economic evaluations of drug and alcohol treatment interventions. They have estimated the cost of specific treatment services,[34,35] estimated the cost per person of various treatment modalities,[29] and evaluated the lifetime costs and benefits associated with methadone treatment.[39] In a recent NIDA study, they compared the effect of three alternative methods of collecting staff time allocations on service costs for

methadone treatment.[35] Dr. Zarkin was the PI on a NIAAA grant estimating the cost, cost-effectiveness, and cost-benefit of alternative alcohol treatments in the Combining Medications and Behavioral Interventions for Alcoholism (COMBINE) study.[67-69] On the same study, Dr. Dunlap led the cost-effectiveness analysis from the patient perspective.[70]

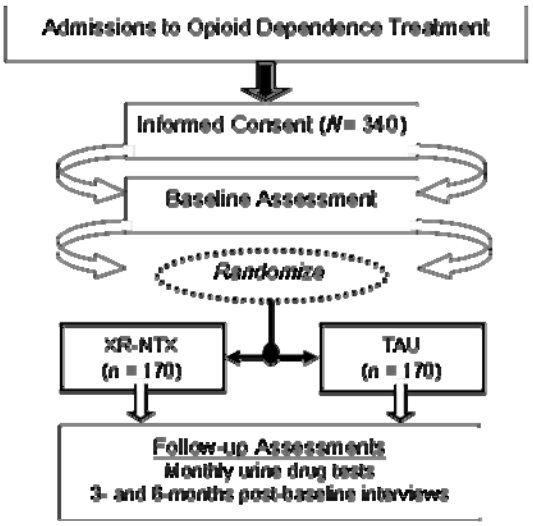
2.4. Environment

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. This research has included two studies of XR-NTX in which Dr. Schwartz collaborated with Dr. Fishman and Mt. Manor Treatment Center. The first was a pilot study[14] and the second is part of a multi-site collaborative R01 led by Dr. O'Brien. Moreover, FRI investigators are currently conducting nine NIDA-supported studies relevant to the present proposal: 1) XR-NTX for probationers; 2) an RCT of IOP v. OP treatment for African Americans receiving buprenorphine treatment; 3) an RCT of buprenorphine for prisoners; 4) NIDA Criminal Justice Drug Abuse Treatment Study; 5) an RCT involving the Re-engineering of Methadone Treatment; 6) an RCT examining entry into comprehensive methadone treatment via interim maintenance; 7) an RCT of SBIRT in New Mexico; 8) Seek, Test and Treat; and 9) the Mid-Atlantic Node of the NIDA CTN. Further description of FRI can be found in Facilities and Resources.

Mountain Manor Treatment Center (MMTC) offers a broad continuum of care for drug-dependent youth which includes buprenorphine detox as well as longer-term buprenorphine treatment, residential, and outpatient treatment.[65] Its well-trained staff includes counselors, nurses and physicians. MMTC has a well-established flow of opioid-dependent youth patients and has successfully conducted two NIDA CTN trials (CTN-0010 and CTN-0028 OROS-MPH trials). It is currently a site in the NIDA-funded study of XR-NTX for adult probationers. In July 2010, the MMTC opioid program for youth won a competitive award for behavioral health innovation from the State Associations of Addiction Services (SAAS) and the Network for Improved Addiction Treatment (NIATx).

2.5. Specific Study Methods

We propose a two-group comparative effectiveness trial in which 340 opioid-dependent youth ages 15-21 will be randomly assigned on a 1:1 basis to receive either XR-NTX or treatment as usual (TAU) for 6 months in the context of a community-based addiction treatment program. Participants will be assessed at baseline, with monthly urine drug tests, and at 3- and 6-months post-baseline to determine: days in treatment; opioid use; other drug (cocaine, marijuana) and alcohol use; criminal behavior and arrests; and relapse to DSM-5 defined opioid use disorder. In addition, changes in HIV risk behaviors and HIV status will be determined. Follow-up at month 7 and 8 will be conducted for the participants who receive the XR-naltrexone injection at month 6, only for safety purposes. Finally, as there are relatively little economic data about substance abuse treatment with youth, we will evaluate the cost, cost-effectiveness and cost-benefits of XR-NTX v. TAU.



Because XR-NTX differs significantly from TAU, not just in terms of the type of medication but also the dosing regimen and treatment process, we will conduct a qualitative examination of the treatment process. Out of the larger sample of 340, 30 or more participants (approximately half from XR-NTX and half from TAU) will complete semi-structured qualitative interviews at baseline, 3- and 6-month follow-ups. In addition, we will recruit a parent or guardian for each of the participants, when possible, to complete semi-structured interviews at each of the same three time points.

2.6. Study Design Issues

We have conceptualized this study as a comparative effectiveness trial conducted under “real world” conditions. For this reason, we have chosen to compare XR-NTX to TAU in an experienced community treatment program. An alternative approach would have been to conduct the equivalent of a Phase II efficacy trial with random assignment to XR-NTX or, say, buprenorphine maintenance. We believe such a study is premature as there is only one report of XR-NTX treatment in youth[13] and buprenorphine maintenance cannot be considered the gold standard for treatment in this population. Furthermore, good clinical practice in the community would use buprenorphine for an individualized length of time based on the physician’s judgment and the patient’s wishes, as reflected in clinical practice in our TAU. We also considered a placebo condition but felt that because most participants were likely to test the naltrexone blockade with self-administered opioids, they would in most cases quickly realize they were assigned to placebo. Moreover, a placebo control condition could be considered by some as unethical given that opioid agonists have proven efficacy in adults.[71] Alternatively, we considered conducting a multi-site Phase IV type trial without a

comparison condition, but we decided that our proposed approach is preferable as it is a more rigorous design with random assignment to a comparison condition. A multi-site trial would increase sample size, but the additional cost and complexity of a multi-site trial is premature, given the state of knowledge regarding the relative effectiveness of XR-NTX as well our ability to recruit a relatively large sample in a single-site study. Finally, we considered including only participants less than 17 years old because FDA labeling permits XR-NTX's use in 17 year olds. However, as noted in Background (above), there are very limited data on effectiveness of XR-NTX in the proposed age group, a population that differs from adults in important aspects such as maturity, vulnerabilities, and treatment responsivity, making the proposed age range optimally informative.

2.7. Participants

A total of 340 male and female participants, ages 15 to 21, inclusive, will be recruited. We anticipate that participant characteristics will mirror MMTC's patient data from calendar year 2010, during which time 60% of their patients were male; their mean age was 18.3; 87.4% were white, 6.8% African American, and 2.9% Hispanic. Among opioid-dependent patients, 46.1% were heroin-dependent and the remainder was dependent on prescription opioids (chiefly oxycodone). We anticipate admitting, on average, 1¾ participants per week (approximately 7 per month) and expect to complete participant recruitment in approximately 195 weeks (3¾ years), yielding a total sample of 340 (= 1¾ participants/week * 195 weeks) participants.

2.8. Inclusion Criteria

1) Meets DSM-5 criteria for opioid use disorder; 2) Receiving treatment for opioid withdrawal at Mountain Manor Treatment Center or elsewhere prior to direct transfer to MMTC; 3) Age between 15 and 21, inclusive; 4) Able and willing to provide informed consent to be randomly assigned to XR-NTX or TAU; and for participants under 18 years of age, parental or guardian consent and participant assent.

2.9. Exclusion Criteria

1) Liver function test levels (Alanine Transaminase, Aspartate Transaminase) four times greater than normal; 2) Unstable medical or psychiatric illness (e.g., schizophrenia) that might make participation hazardous; 3) History of serious suicide attempt in the past 6 months; 4) History of allergic reaction to naloxone, and/or naltrexone; 5) Current chronic pain condition for which opioids are deemed necessary for ongoing care; 6) blood coagulation disorder (e.g., hemophilia); 7) Body Mass Index > 40; and 8) If female, pregnant, lactating, unwilling or unable (due to parental objection) to use FDA-approved contraceptive methods; 9) and needing detoxification from benzodiazepines during treatment at Mountain Manor.

Qualitative Sample. In order to achieve a diverse range of respondents in terms of age, gender, and drug of abuse, purposive sampling will be used to select 30 or more participants (approximately half from XR-NTX and half from TAU) to complete semi-structured qualitative interviews. In addition, because treatment adherence for youth is often influenced by their parents, we will attempt to recruit a parent or guardian for each

of the qualitative sample participants, to be interviewed at each of the same three time-points.

2.10. Recruitment

Opioid-dependent patients in withdrawal are typically started on a buprenorphine taper at MMTC. Consistent with practice in the US and with the American Society of Addiction Medicine Patient Placement Criteria, this taper is provided on the residential unit or through the outpatient clinic, depending on the patients' psychosocial stability and insurance coverage. MMTC typically admits 6 youth per week who require treatment for opioid withdrawal symptoms and, as is currently standard practice at MMTC, consent is obtained from all new admissions in order to review their charts and determine eligibility for possible research inclusion. Compared to adult patients, there are very few youth patients who present with chronic pain/ pain management treatment as a primary source of opioid dependence. Study physicians will evaluate potential participants, coordinating with outside care providers, and exclude from participation any patients with a current chronic pain condition for which opioids are deemed necessary for ongoing care. MMTC patients who completed opioid detoxification in a setting outside MMTC just prior to MMTC admission will also be screened to determine their study eligibility. To enhance recruitment, we will distribute information about the study in the community, including school-based health clinics, adolescent STD clinics, the city's substance abuse authority, and the four other adolescent drug treatment clinics it funds.

During the course of the first few days of buprenorphine taper, medical staff meet with patients and their parents (as appropriate) to discuss treatment options. Research staff will then present an overview of the study to the parents of these new admissions (for those under 18 years of age) and to the patients, themselves, to determine potential interest in study participation. Patients who express interest in participating (and for those under 18 years old, their parents) will meet with the RA to discuss the study further and to be screened for eligibility. Screening for eligibility will include review of Mountain Manor treatment records to determine initial eligibility. Individuals who screen as eligible will be offered an initial informed consent, which 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). Adolescents who decide not to participate will receive regular clinical care at MMTC, which involves an individually-determined course of treatment.

The study physician will meet with potential participants (and their parents, as appropriate), review the treatment alternatives to participation, as well as the study's risks and benefits. They will be informed that during the course of the study, they should report any concerns regarding study medication to the medical staff at MMTC through a 24-hour phone number. The informed consent process will include a consent quiz that will be re-administered up to three times until a score of 100% is achieved. Potential participants who are unable to score 100% on the consent quiz will not be eligible for participation.

As necessary, the consent process will be conducted by telephone with adults. In such cases the adult participant, parent or legally authorized representative, will receive a copy of the consent document(s) in advance so they can familiarize themselves with the

consent form(s). The RA will then conduct the informed consent discussion by telephone, assuring adequate time to address questions, concerns, and to ensure adequate comprehension of the consent and the study information. Parents completing consent forms concerning their minor children's study participation will then complete an IRB approved consent quiz to verify comprehension. Parents completing the consent process regarding their own participation in the qualitative interviews will not complete a consent quiz. The signed and dated consent document(s) may be returned to the research staff by e-mail, facsimile or mail for the researcher's signature and date. This process will be completed before any research procedures begin.

2.11. Baseline Medical Screening

As is standard practice upon admission to MMTC, medical staff conduct a history and physical exam which includes a neurological and psychiatric assessment, as well as an assessment for coagulopathy (e.g., hemophilia by family history). In addition, staff will draw blood to test liver function and screen for hepatitis C and HIV, and test for pregnancy in females. The study physician will review the laboratory test results for inclusion/exclusion criteria. Individuals excluded for medical or psychiatric reasons will be provided appropriate treatment or referral for follow-up to treat the reason for exclusion. Individuals who meet inclusion criteria will receive study assessments described below, their relevant medical screening record to demonstrate meeting inclusion/exclusion criteria will be included in the research record, and they will be randomly assigned to XR-NTX or TAU.

2.12. Random Assignment

The RA will administer the assessments at study entry, after which the RA will contact the project manager to obtain the participant's assignment to study condition through the use of a block randomization procedure in which, for each successive block of 4 participants within each gender, 2 will be assigned at random to the XR-NTX Condition and 2 will be assigned to TAU. Only the project manager and PI will have access to the random assignment table. We propose randomly assigning participants to Condition while they are receiving buprenorphine for opioid withdrawal because that approach mirrors how the treatments (XR-NTX and TAU) are delivered in clinical practice. Had the proposed study been a Phase 2 efficacy trial rather than a comparative effectiveness trial, we would have proposed randomly assigning participants to Condition only after they were detoxified and opioid-free for at least seven days. However, we rejected that approach for the present study because in normal clinical practice a patient who was to receive buprenorphine for longer than a brief dose taper would not be tapered with buprenorphine, maintained off medication for 7 days, and then re-started on it.

2.13. Qualitative Sample Selection

Purposive sampling, a non-random process by which participants are selected in order to achieve a certain goal (in this case, diverse patient characteristics), will be used to select 30 or more participants (approximately half from XR-NTX and half from TAU) to complete semi-structured qualitative interviews. A broad range of respondents will be selected with respect to age (approximately half from the teenage range (15-19 age range), gender (approximately equal numbers of females and males), and drug of

abuse (prescription opiates and other drugs). For each youth participant, we will attempt to recruit a parent or caregiver of that youth, who will also be interviewed. Efforts will be made to include both mothers and fathers in this subsample but inclusion will be based both on their willingness to participate and the scope of their involvement in their child's life. The total qualitative sample will consist of 60 or more participants: 30 or more adolescent patients and one parent or caregiver for each patient, whenever possible. The proposed sample size will ensure that the data set is complete (as indicated by information replication or redundancy) and should allow for the extraction of sufficiently meaningful qualitative data in which details concerning context and intention are included along with directly verifiable information.[72,73]

2.14. XR-NTX Condition

Participants randomly assigned to XR-NTX will complete the buprenorphine dose taper (or will have already completed the detoxification process at another location), initiated prior to their study enrollment, over approximately 5 days either as an inpatient or outpatient, depending upon their psychosocial stability and insurance status in keeping with the ASAM Patient Placement Criteria. After a minimum of 6 days without buprenorphine or other opioids, they will be administered an on-site urine test for opioids (including morphine, oxycontin, methadone and buprenorphine). In keeping with standard practice over the past 4 years at MMTC (see Preliminary Studies), those with a negative test will be given oral naltrexone lead-in over 3 days (6.25 mg, 12.5 mg, and 25 mg) under MMTC medical staff supervision. For cases in which the patient is unable to stay for the full 3-day period, oral naltrexone will be administered over 2 days, with an initial dose of 6.25 mg and a second dose of 25 mg. Individuals who do not have opioid withdrawal signs or symptoms within 2 hours of administration of the 25 mg oral dose naltrexone will be given an intramuscular injection of XR-NTX [Vivitrol®] at a dose of 4cc (380mg of naltrexone)]. Participants who have side effects from protracted opioid withdrawal after XR-NTX administration, such as insomnia, may be treated with ancillary medications at the discretion of the treating physician, as would normally occur in clinical practice. Vivitrol® is FDA-approved for the prevention of relapse to opioid dependence for adults, hence an IND will be obtained from the FDA for the treatment of the age range that the FDA deems to be pediatric age (we believe this will include 15-16 year old participants).

Individuals assigned to XR-NTX will have a dose administered to alternating sides of the buttocks every four weeks for up to 6 months. At the conclusion of study participation at the 6-month follow-up, the MMTC medical staff will offer the participants the option of continuing with XR-NTX, to discontinue the medication, or to receive any other treatment option then available. All participants assigned to XR-NTX will receive psychosocial treatment as described below.

2.15. Treatment-as-Usual (TAU) Condition

Participants randomly assigned to TAU will participate in the standard youth opioid program at the treatment center (or at a treatment program closer to the participants home if they are unable to return regularly to MMTC). This will include choice of medication-free treatment or buprenorphine at the discretion of physicians, patients and families. The patients will complete their buprenorphine taper or be re-started on

buprenorphine (if they have already completed detoxification and opt to re-start buprenorphine treatment), or remain on buprenorphine during the 6 months of the study for as long as they and their physicians think is appropriate (in keeping with usual clinical practice). Participants remaining on buprenorphine will have their dose adjusted in response to self-report of craving and opioid use as well as urine drug testing results. The general target dose will be 12-20 mg buprenorphine per day. Participants will see the physician for a brief medication check visit on a weekly basis and at the outset of treatment will receive a one week supply of medication by prescription. The frequency of physician visits and the amount of medication provided through prescription will be adjusted during treatment in response to the patient's progress. As they stabilize, patients will reduce the frequency of medical visits from weekly, to every other week to monthly as they demonstrate drug and alcohol abstinence, psychosocial stability and the ability to manage their medications properly (e.g., not "losing" their prescriptions or medications). Participants will have the opportunity to taper off the medication over the course of several weeks or, during the course of treatment, to receive any other treatment option available to patients at MMTC (except XR-NTX). All participants in TAU will receive psychosocial treatment as described below.

2.16. Concurrent Psychosocial Treatment for both XR-NTX and TAU Conditions

All participants, regardless of treatment condition, will be offered the same level and type of psychosocial treatment consisting of 60-minute group counseling sessions, guided by the counseling manual used by MMTC for the CTN Buprenorphine Study for Opioid Dependent Youth (CTN 0010). This manual is based on Group Drug Counseling for Adolescents and Young Adults in Recovery for Opioid Dependence (see Appendix)[74] and adapted specifically for treating opioid-dependent adolescents by George Woody's group at the University of Pennsylvania. Individual counseling will also be once per week and will be guided by the manual Cognitive Behavioral Therapy for Adolescent Substance Use Disorders[75] used in the NIDA CTN study of substance-abusing adolescents with co-morbid ADHD, for which MMTC was a study site. The manual consists of 16 sessions, including 2 family sessions and features behavioral, cognitive-behavioral, and motivational enhancement techniques. MMTC staff is experienced in using both these manuals and have found them appropriate for this patient population. Less frequent appointments will generally be needed in the following weeks/months depending on treatment response and individual participant's needs.

Family treatment services are offered to educate families about opioid addiction, to obtain their support for participation in treatment, to reduce negative family dynamics that may interfere with the goals of treatment, and to respond to crises. Self-help meeting attendance is encouraged, and attention in counseling is given to dealing with and responding to the stigma that may be associated with pharmacotherapy use by patients attending 12-Step meetings.

2.17. Return to Treatment Following Dropout from XR-NTX or TAU

Participants who drop out of treatment will be encouraged to return to treatment. Those who were not clinically responding to their assigned treatment prior to dropout may choose to either resume their assigned treatment or to receive any other treatment

option available on-site or off-site by referral during the study. Additionally, Participants who fail to receive their allocated intervention will also be followed throughout the study.

Follow-up and Attrition. Consistent with our prior research with opioid-dependent patients, we will collect detailed locator information, including cell phone numbers, email addresses, social media contact information, parental and peer contact information, as well as names and addresses of places in the community that they frequent. When unable to contact participants via phone or email, the RAs will track the participants in the community. We have established successful and robust procedures for participant tracking, and have routinely obtained follow-up rates in excess of 90% among a variety of drug-dependent populations. Thus, we understand how to effectively track and conduct follow-up assessments with this often hard-to-reach population and expect to obtain follow-up rates well above 85%. However, in order to remain conservative, our power analyses (see, Power, below) will assume an 85% follow-up rate. To support our follow-up goals, we will include contingency management reinforcement for follow-up visits attended and completed in-person. Using a fishbowl type lottery participants will have an opportunity to win a prize for each follow-up visit completed face-to-face with the RA. A range of prizes will be available to win, with a maximum prize not to exceed $100 in value.

2.18. Assessment Plan: Baseline and Outcome Measures

The measures described below and shown in Figure 1 will be administered at baseline and at 3- and 6- months post-baseline. Participants will receive $30 in cash for completing the baseline interview (at study entry), and the longer 3-, and 6-month follow-up assessments. Participants will be paid $20 in cash for each shorter visit during months 1, 2, 4, and 5 (and 7 and 8, if the participant receives an XR-naltrexone injection in month 6), which include providing urine samples and brief follow-up interviews. The total amount of money that a participant can receive if he/she completes all of the shorter and longer interviews is $170 (with an additional $40 if he/she completes the month 7 and 8 interviews). Participants who attend and complete follow-up visits in-person will have the opportunity to participate in a fishbowl type lottery drawing for the opportunity to win a range of prizes, with the maximum prize not to exceed $100 in value. In addition, if the participant is chosen and agrees to participate in the additional in-depth interviews, he/she will receive $30 in cash for each of the three completed interviews for a total of an additional $90. Self-report instruments have been carefully selected based on their history of use in clinical research and demonstrated reliability and validity.

2.19. Measures for Aim 1

Days in Treatment. The number of days retained in treatment will be operationally defined as the number of days from study enrollment until drop-out from treatment or 6-month follow-up (whichever comes first). This information will be obtained from study records as we have successfully done in our prior research.[13,57,58,60]

Self-reported Opioid and Other Drug and Alcohol Use (Time Line Follow Back). Participants will be asked at each assessment point about the number of days using opioids (heroin and prescription opioids) and other drugs (including cocaine and

marijuana) and alcohol use using the time line follow back (TLFB) technique used in the CTN 0010 study.[7]

Urine Drug Testing. Participants will have urine samples collected at baseline and monthly thereafter, regardless of whether they remain in treatment. The baseline visit samples will be sent to a certified laboratory for testing by Enzyme Multiplied Immunoassay Test (EMIT) for opioids (including buprenorphine, oxycontin), marijuana, cocaine and benzodiazepines. Methadone data will be analyzed prior to XR-NTX induction and at monthly follow up visits as well as for other illicit drugs. Buprenorphine-positive tests for patients not enrolled in treatment will be considered as opioid-positive (but not considered positive for patients enrolled in buprenorphine treatment).

Criminal Activity and Arrest. Questions on criminal activity and arrests will be asked using time line follow back techniques at each assessment point and will be drawn from the brief Friends Research Institute's supplemental questionnaire which has been used extensively in research with opioid dependence.[76,77]

Drug Abuse Diagnoses. We will use the CIDI-2 Substance Abuse Module (modified by adding the craving criterion in the DSM-5) to determine DSM-5 criteria for opioid use disorder during the one month period prior to their baseline and 3- and 6-month follow-up assessments. Although DSM-5 opioid use disorder is an inclusion criterion, we will also administer the CIDI-2 at baseline in order to examine changes in symptoms. The CIDI-2 is used in both epidemiologic studies and as an outcome measure in drug abuse treatment trials.[78] It will provide important and novel data that is complementary to the use of self-reported drug use and of urine testing data, and it will be a measure of impairment associated with any ongoing drug use. The CIDI-2 is a fully structured interview[79] that has excellent reliability in diagnosing respondents with drug dependence[80,81] and was used in the PI's study of IOP v. OP with buprenorphine treatment.

Figure 1. Data Collection Schedule & Measures by Aim

Measures	Baseline	Follow-up
***Aim 1*: To compare XR-NTX v. TAU on: days in treatment, opioid and other drug and alcohol use, criminal activity and arrest, and DSM-5 Criteria for opioid dependence.**		
Days in Treatment		6-month
Self-reported Opioid and Other Drug and Alcohol Use (TLFB)	◆	3- and 6-month
Urine Drug Testing	◆	Monthly
Criminal Activity and Arrest (TLFB)	◆	3- and 6-month
DSM-5 Opioid Use Disorder (CIDI-2 SAM)	◆	3- and 6-month
Aim 2: To examine the impact of XR-NTX on HIV drug and sex risk behaviors.		
HIV Risk Behavior (RAB)	◆	3- and 6-month
HIV Testing	◆	6-month
Aim 3: To evaluate the cost, cost-effectiveness, and cost-benefit of XR-NTX v. TAU among opioid-dependent youth.		
Short Form-12	◆	3- and 6-month
Economic Form 90	◆	3- and 6-month
Substance Abuse Services Cost Analysis Program (SASCAP)†	◆	†
Supplemental Measures		
Expectation for Treatment Duration	◆	
Number of Counseling Hours Received		Monthly
Hepatitis C Test Results	◆	6-month
Quality of Life (WHOQOL-BREF)	◆	3- and 6-month
Treatment Preference Questionnaire	◆	
Patient Course of treatment Questionnaire (patient version)		1-month
Safety and Adverse Event Reporting		
Adverse Event Report Form	◆	Monthly
Adverse Event Report Form for participants who receive XR-NTX at month 6		7- and 8-month
History and Physical Examination including neurological, psychiatric, and coagulopathy assessment	◆	
Beck Depression Inventory-II	◆	Monthly
Benzodiazepine Detoxification Required	◆	
Liver Function Tests (ALT and AST)	◆	3-month for all participants and at 1 month and 6 months for anyone receiving XR-naltrexone in the prior month
Pregnancy Test	◆	Monthly on all females
Pregnancy Outcome Questionnaire		Following birth, miscarriage or termination of pregnancy (for applicable females only)
† Consistent with prior research, the SASCAP will be administered once during the treatment phase		

2.20. Measures for Aim 2

Risk Assessment Battery (RAB). The abbreviated RAB will be administered at each assessment point. It is a brief questionnaire covering substance use and sexual HIV risk behaviors that has been extensively used with drug dependent populations,[82] including adolescents.[83] The scale's drug-use risk and sex risk scores will be used as outcome measures.

HIV Testing. Baseline and 6-month HIV testing will be conducted by a certified laboratory with blood samples collected by the MMTC staff. The laboratory will screen for HIV 1 and 2 with an ELISA test and screen positive samples will be confirmed with Western Blot. Participants will have pre- and post-test HIV counseling. [While we do not expect significant changes in HIV infection status between baseline and 6-month follow-up, we are including this test as an additional assessment of HIV risk.]

2.21. Measures for Aim 3

Short Form-12 (SF-12). We will use SF-12 and the SF-6D system to measure quality of life and to estimate quality-adjusted life-years (QALYs) associated with the alternative treatments.[84] SF-12 is a shorter version of the SF-36 and is designed to measure overall physical and mental health status for individuals age 14 years and older. All participants completing the SF-12 questionnaire can be assigned an SF-6D score (a continuous outcome score on a scale of 0.30 to 1.00 [full health]) to generate a preference-based single index measure and obtain QALYs for use in cost utility analysis.[84,85]

Economic Form 90. This survey form will be modified to collect data on economic outcomes of health utilization, crime, and employment/school enrollment status at each assessment point. It is a modified version of the Form 90 family of instruments originally designed to collect alcohol use and economic outcome data for alcohol treatment studies.[86-89] It collects data on inpatient, outpatient, and ER utilization; criminal behavior including number of arrests and nights incarcerated; labor market information including employment status, wage at current job frequency of work, and amount of money received beyond paid employment; and school enrollment status and educational attainment. In addition, the form collects information on the costs incurred by patients in receiving their treatment intervention.

Modified Substance Abuse Services Cost Analysis Program (SASCAP). Provider-level costs for the treatment interventions will be estimated using the SASCAP approach,[34] modified specifically for the interventions under study. The SASCAP[90] consists of a provider questionnaire to collect activity-level resource use and cost data for treatment staff, consultants and contracted services, building space, equipment, supplies and materials, and other miscellaneous resources (e.g., utilities, training expenses). The SASCAP method reliably estimates the costs of specific treatment activities and the total cost per patient, and Dunlap et al.[70] and Zarkin et al.[35,39,91] have applied this micro-costing approach in other studies, such as the Cutting Back intervention[91] and the COMBINE study of alcohol treatments.[67,68,70]

2.22. Supplemental Measures

Expectation of Treatment Duration. Patient expectations regarding treatment preference and duration will be asked at baseline using the brief questions from PI Mitchell's study of IOP v. OP in buprenorphine treatment. The RA will emphasize that the participants' responses will not be shared with clinical staff. The RA will collect information regarding discharge treatment received through clinic records. The Discharge Doctor's version of the Patient's Course of Treatment Questionnaire will be collected when the participant discharges from MMTC inpatient treatment. The RA will also administer the Patient's version of the Patient's Course of Treatment Questionnaire at the month-1 visit. These measures will be used in supplementary analyses to determine the relationship between expectations of treatment duration and patient outcomes by treatment condition, as briefer planned sojourns may be associated with worse outcomes.

Number of Counseling Hours Received. These data will be collected by research staff from applicable clinic billing records. It will be examined in supplementary analyses to determine its relationship to patient outcomes by treatment condition.

Hepatitis C. We will also examine the change in infection status for hepatitis C. Although we do not anticipate significant changes (as hepatitis C infection often occurs shortly after initiation of drug injection),[92,93] there are limited data on hepatitis C seroconversion among opioid-dependent youth in different drug abuse treatments. Blood will be drawn for hepatitis C testing at baseline and 6-month follow-up.

Quality of Life (WHOQOL-BREF). The World Health Organization Quality of Life – BREF comprises 26 items, which measure the following broad domains: physical health, psychological health, social relationships, and environment. The WHOQOL-BREF is a shorter version of the original instrument and is better suited for use in large research studies or clinical trials.

2.23. Adverse Event (AE) Reporting

Depression, liver functioning (ALT and AST), and pregnancy (in female participants) will be assessed prior to treatment admission. The 21-item BDI, which has been used extensively, including among youth,[94-97] will be administered as a baseline assessment and repeated monthly at the same time as urine collection for drug testing to screen for depression and suicidal ideation.

Female participants on study medications will be asked monthly about their last menstrual period and administered a urine pregnancy test monthly. Liver function will be assessed again for all participants at 3-month assessment to provide additional safety data and at months 1 and 6 if the participant receive XR-naltrexone in the previous month. Finally, adverse event reports will be taken monthly at the time of the drug test by the RA on all participants using the AE Report Form, which will be coded using the Medical Dictionary for Regulatory Activities (MedRA) system.[98] In addition, the AE form will be administered (by telephone, if necessary) for those participants who receive the XR-naltrexone injection at month 6.

2.24. Process Interviews

Semi-structured qualitative interviews will be conducted with a sub-sample of participants in both Conditions at baseline, 3-, and 6-month follow-ups to examine treatment expectations, experiences and satisfaction with the medication (including social stigma and any side-effects experienced), views concerning dosing and other aspects of medical treatment, utilization of psychosocial services, current drug use, and issues related to treatment retention. The interview content for patients and their parents/caregivers will overlap considerably, so as to provide an opportunity for a direct comparison of stakeholder perspectives.

2.25. Analyses for Aims 1 and 2

Aim 1: To determine the relative effectiveness of XR-NTX compared to TAU for opioid-dependent youth in terms of the following 3- and 6-month outcomes: a) days in treatment; b) opioid use; c) other drug (cocaine and marijuana) and alcohol use; d) criminal behavior and arrests; e) relapse to DSM-5 defined opioid use disorder.

Hypothesis 1A: Participants in XR-NTX Condition will be retained in treatment longer than those in TAU.

Hypothesis 1B: Participants in XR-NTX will have lower rates of heroin and prescription opioid and other drug use, alcohol use, criminal behavior and arrest, and opioid dependence criteria.

Aim 2: To examine the impact of XR-NTX on HIV drug- and sex-risk behaviors at 3- and 6-month follow-up, and HIV infection status at 6-months.

Hypothesis 2: Participants in the XR-NTX will be less likely to use other drugs and will therefore report lower HIV drug- and sex-risk behaviors.

Outcome Measures. Outcome variables will be of three distinct types: 1) discrete random variables (e.g., number of days in treatment), assumed to follow a Poisson distribution; 2) dichotomous variables (e.g., urine drug test results for opioids and other drugs), assumed to follow a binomial distribution; and, 3) continuous random variables (e.g., RAB scale scores), assumed to follow a normal distribution.

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

Treatment Variables. There will be a single treatment variable: Treatment Condition (XR-NTX v. TAU).

Control Variables. Two additional predictor variables – participant age and gender – will be included as "main effects" in all analyses in order to examine for potential differences in treatment outcome as a function of these two participant characteristics. The interaction between Treatment Condition and each of these participant characteristics will also be estimated and tested for significance. These interaction effects test the extent to which responsiveness to Treatment Condition varies as a function of age and/or gender.

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 Group factor. (For a summary of assessment time points for each outcome, see Figure 1, above.).

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

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

Power

To acknowledge the possibility that there might be 2 equally-spaced interim analyses, α will be set equal to .0379, based on the O'Brien-Fleming spending function,[99,100] for the test of all effects. Power for the primary outcome of number of days in treatment, assumed to follow a Poisson distribution, does not involve a Time effect, as it is measured at the conclusion of the 6-month treatment period. Assuming the base rate exp(∃) for TAU and odds ratio for XR-NTX of 1.15, power (1 – β) = .80. This odds ratio implies a 15% difference in number of days retained in treatment between the two treatment conditions.

Stroup[101,102] has outlined a comprehensive four-step procedure to estimate power that can be applied to GLiMMs. This procedure was implemented in the current case, and

involves estimation of power using a variety of covariance structures for the Time (T) effect. Heterogeneous covariance structures were defined in all three cases, in which the variance component at T1 (baseline) was arbitrarily set at 1, at T2 (3-month follow-up) was specified as 90% of the variance of Time 1, while at T3 (6-month follow-up) was specified as 95% of the variance of T2. This pattern reflects the frequent occurrence that groups become more homogeneous over time following an intervention. Correlation over Time was specified as .6 for the compound symmetric heterogeneous structure. The correlations of adjacent time points were set to .6 for the first-order autoregressive structure, thereby setting the T1–T3 correlation to .36. For the UN case, the T1-T2 correlation was specified as .8, T2-T3 as .7, while T1-T3 as .6. This pattern was chosen to acknowledge the change in variances over Time (which thereby reduces the corresponding correlations). Second, two datasets were created, assuming the dependent variable was (1) continuous and normally distributed or (2) binary and distributed binomially, respectively. In each dataset (1), the mean of the TAU condition was set at 1, .8, and .9 at T1-T3, respectively, indicating a small treatment effect associated with TAU at 3 months, then with an expected decrement in success at 6 months, while the means for the XR-NTX condition was set at 1 at T1, and then set to .5 at 3 months, indicating a medium treatment effect, with the mean set to .65 at T3 to reflect a small-to-medium effect, again taking into account an expected decrement. Similar procedures were followed for dataset (2). The only non-null effect in each dataset was the hypothesized effect of interest. Thus, simulations were conducted under what might be considered "worst-case scenarios." Finally, observations were dropped from the data consistent with the expected loss of approximately 10% of participants at T2 and an additional 5% at T3 (see Follow-up and Attrition, above). Therefore, in each dataset, 34 (approximately 10%) of the observations were chosen at random and their observations at T2 and T3 were dropped. An additional 17 of the observations at T3 were chosen at random and dropped. Hence, power was estimated for a design in which the effects were unbalanced in a manner similar to what is expected in the proposed research. Resulting power to test all hypotheses exceeded .9 in most simulations, except, not surprisingly, for an unstructured covariance matrix, for which power fell into the low .80s.

From a more rudimentary perspective, power calculations based on the set correlation method[103,104] for a multivariate multiple-groups profile analysis can be used to calculate reasonable estimates of power for the primary outcome measures under the assumption they are normally distributed, with the estimates likely to be conservative in the case of Poisson or binomial outcome variables. Under the extremely limiting assumption that no other effect in the model was significant, and assuming N = 289 [= 340 – 51 (15% of the sample) to conservatively account for attrition] and $\alpha = .0379$, an effect size in the population of $f^2=.0365$ associated with Treatment Condition X Time interaction effect would yield a power of .8 for that effect. This effect size falls in the "small" range, with $f^2=.02$ considered a "small" effect and $f^2=.15$ a "medium" effect.[104] In other words, and imprecisely, under the assumption that the effect in the population was ≥ .0345 (or, alternately, that the population semi-partial r^2 associated with the Treatment Condition X Time effect was ≥ .0351), there is 80% chance of concluding that effect is significant if α is set to .0379 and 289 participants complete the trial.

2.26. Supplementary Analyses

Various follow-up and ancillary analyses will be considered, based on the results of the analyses of the primary outcome variables. In addition to the supplemental analyses mentioned above regarding treatment preference, treatment expectations, and the number of counseling sessions received, there are three sets of additional analyses that we intend to conduct. First, as noted in Study Design Issues (above), we intend to re-fit our statistical models, including Primary Drug of Abuse (heroin v. prescription opioids) and its interaction with Treatment Group to examine, on a post hoc basis, whether Primary Drug of Abuse moderates treatment effectiveness. Second, examination of the use of illicit drugs other than opioids, particularly cocaine and marijuana, at treatment entry may help to explicate the extent to which the use of such other drugs plays a role in treatment outcome. Third, it may be important to examine number of days in treatment from the perspective of a survival model, because such an analysis may lead to a better understanding of time-dependent barriers that lead to early dropout from treatment (e.g., if there is decided attrition in the XR-NTX group after three months, it would suggest an examination of treatment impediments that might exist following 90 days of treatment).

2.27. Analyses for Aim 3

Aim 3: To evaluate the cost, cost-effectiveness, and cost-benefit of XR-NTX v. TAU among opioid-dependent youth.

Hypothesis 3A: The XR-NTX condition will have higher costs per person relative to the TAU condition.

Hypothesis 3B: XR-NTX will yield better outcomes relative to TAU in terms of increased retention in treatment, reductions in opioid use and other substances (e.g. cocaine, alcohol, marijuana), reductions in criminal behavior, and improvements in quality of life (i.e., QALYs) to justify its greater costs; thereby resulting in XR-NTX being cost-effective relative to TAU.

Hypothesis 3C: XR-NTX treatment will yield greater economic benefits in terms of criminal activity and health care utilization in the 6-month follow-up period relative to its costs than the TAU condition.

Cost Analysis. We will derive cost estimates for various treatment activities following an activity-based approach.[41] The labor costs of each activity are equal to the product of the amount of time spent by each person on the activity and their hourly wage. We will obtain space costs from Mt. Manor. We will estimate space costs as the average square footage of rooms used multiplied by the determined market rent per square foot. To estimate medication costs, we will use data from the study team and information obtained from published literature. Finally, we will multiply the unit cost of other treatment resources (e.g., laboratory tests) with the quantity used per treatment session. The total treatment cost for each patient is simply the cost per activity multiplied by the number of activities or services received by the patient during treatment, and taking the mean across patients in a given treatment condition yields the mean per patient cost of that treatment.

Cost-Effectiveness. Our CEA methodology follows the approach described in the literature[85,105] and that has been implemented in Zarkin et al.[35,106,107] and Dunlap, Zarkin, et al.[70] in the context of randomized controlled trials. For the proposed economic aim, we will combine the appropriate cost estimates described above with the associated treatment effectiveness measures (e.g., substance use, crime, treatment retention). Separate cost-effectiveness analyses will be conducted for the primary outcomes of substance use, criminal behavior (e.g., number of arrests), and treatment retention. The incremental cost-effectiveness ratio (ICER) is calculated by dividing the difference in costs of two alternatives by the difference in their effects of the two alternatives. The estimated ICER can be interpreted as dollars spent per unit of desired outcomes gained (e.g., $5,000 per QALY gained). To gauge the sampling uncertainty of the estimated ICERs, we will calculate the confidence intervals via nonparametric bootstrap methods.[108,109] We will also estimate cost-effectiveness acceptability curves (CEACs) using nonparametric bootstrap methods.[35,70,110-112] The CEACs incorporate the inherent variability of the cost and effectiveness estimates and show the probability that a treatment is cost-effective as a function of the policy maker's intrinsic valuation or willingness to pay for the clinical outcome.

Cost-Benefit. We will perform a CBA to examine the monetized benefits relative to costs for XR-NTX versus TAU. The key economic outcomes are crime[113] and health care utilization. Data on these outcomes will be collected through the Economic Form 90 (as described above). Our proposed approach provides reliable data in a less costly manner (compared to administrative claims data) that will fulfill the purposes of this study. First, we propose to collect data for a relatively short time period which should help minimize recall bias. Second, because the purpose of our economic aim is to compare differences in costs and consequences between the alternative interventions, the likelihood of misreporting bias should be similarly distributed in each of the randomized study arms with minimal impact on difference calculations. The unit costs to be used in monetizing these economic outcomes will be drawn from various literature and public data sources.[69,114-116]

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

2.28. Qualitative Data Analysis

Qualitative data will be collected to augment the clinical trial and aid in the understanding of the treatment process from the patient's perspective. 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[117-120] and this strategy will be applied to the current study.

3. STUDY ISSUES

We are aware that the study's generalizabilty may be limited by the fact that the study is being conducted at a single site. However, we believe that a multi-site trial is premature given the state of knowledge regarding the effectiveness of XR-NTX with youth. Additionally, the inclusion of a real-world setting, drawing from the standard patient flow of an experienced community treatment provider who treats a broad range of patients (from public funding including Medicaid to commercial insurance) will enhance its relevance to a broad clinical audience. A second potential concern involves not including patient drug of choice (heroin v. prescription opioids) as a moderating variable in a main hypothesis. The limited empirical data currently available made it difficult to form a hypothesis regarding differential responsiveness to the two treatment conditions as a function of opioid of abuse. Therefore, we decided to explore this relationship as part of Supplementary Analyses rather than as an additional primary Aim. Finally, rather than limiting study participation to those under 18 years of age, we chose to broaden our sample to include youth 15-21 years of age since this age group fits clearly within most definitions of youth,[121-123] including that used by NIH.

4. DISSEMINATION

We will publish our findings in the scientific literature and present at recognized national and international meetings. Locally, we will keep the Directors of the city's substance abuse authority and the Maryland Alcohol and Drug Abuse Administration (both of whom strongly support the study, see Letters of Support) up-to-date regarding the study and its implications. At the national level, we will work closely with CSAT's National Addiction Technology Transfer Center, the National Association of State Alcohol and Drug Abuse Directors, and the American Society of Addiction Medicine to ensure dissemination of the study's progress and findings. We will share study findings with the national CTN's treatment program directors and investigators. Finally, the investigators will work closely with NIDA Notes staff in order to communicate findings to the field.

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6. HUMAN SUBJECTS

6.1. Study participants

Study participants will include 340 youth and a subset of 30 of the youth's parents. Unless otherwise specifically stated, human subject information contained below will refer to the youth participants, and the term participants will refer to youth participants.

Youth Participants

Participants will be 340 male and female opiate-dependent youth ages 15–21 years of age in the Baltimore metropolitan area who are new admittances to Mountain Manor Treatment Center (MMTC) for opioid dependence treatment.

Inclusion Criteria. 1) Meets DSM-5 criteria for opiate use disorder; 2) Receiving treatment for opioid withdrawal at Mountain Manor Treatment Center or completing opioid withdrawal treatment elsewhere just prior to admission to MMTC; 3) Age between 15 and 21, inclusive; 4) Able and willing to provide informed consent to be randomly assigned to XR-NTX or TAU; and for participants under 18 years of age, parental or guardian consent and participant assent.

Exclusion Criteria. 1) Liver function test levels (Alanine Transaminase, Aspartate Transaminase) four times greater than normal; 2) Unstable medical or psychiatric illness (e.g., schizophrenia) that might make participation hazardous; 3) History of serious suicide attempt in the past 6 months; 4) History of allergic reaction to naloxone, and/or naltrexone; 5) Current chronic pain condition for which opioids are deemed necessary for ongoing care; 6) blood coagulation disorder (e.g., hemophilia); 7) Body Mass Index > 40; 8) If female, pregnant, lactating, unwilling or unable (due to parental objection) to use FDA-approved contraceptive methods; and, 9) needing detoxification from benzodiazepines during treatment at Mountain Manor.

Individuals excluded for pregnancy, or other medical and psychiatric reasons will continue treatment at Mountain Manor as usual outside the confines of the study and will have access to appropriate obstetrical, medical or psychiatric treatment as needed. These inclusion and exclusion criteria will permit the study to examine outcomes for a wide variety of typical patients who enter drug abuse treatment, yet balance important safety issues (such a pregnancy or hepatic problems) to thereby afford maximum generalizability and safety. Individuals who meet exclusion criteria because of concurrent need for benzodiazepine detoxification will have this drug use disorder addressed during their usual care at MMTC.

We anticipate admitting approximately 1 ¾ participants per week (approximately 7 per month) to the study and expect to complete participant recruitment in approximately 195 weeks. This rate of admission will be well-managed by Mountain Manor Treatment Center (MMTC) as they typically admit 6 opioid-dependent patients per week, thus allowing for the possibility that some treatment seeking individuals meeting inclusion criteria may elect not to participate.

We anticipate that participant characteristics will mirror MMTC's patient data from calendar year 2010, during which time 60% of their patients were male; their mean age

was 18.3; 87.4% were white, 6.8% African American, and 2.9% Hispanic. Among opiate-dependent patients, 46.1% were heroin-dependent and the remainder were dependent on prescription opioids (chiefly oxycodone).

Parent Participants

A subsample of 30 or more parents, one parent or caregiver for each of the youth participating in the qualitative interviews, whenever possible (see below), will be invited to complete semi-structured qualitative interviews. We will attempt to recruit both mothers and fathers in the sample, but their inclusion will be based both on their willingness to participate and the scope of their involvement in their child's life. Demographic characteristics of this parent/caregiver subsample are believed to mirror those of the youth participant sample.

6.2. Recruitment & Informed Consent

Participants will be recruited from newly-admitted opiate dependent MMTC patients, ages 15–21 years of age. To enhance recruitment, we will distribute information about the study in the community, including school-based health clinics, adolescent STD clinics, the city's substance abuse authority, and the four other adolescent drug treatment clinics it funds. The RA, under supervision of the PI, will inform them (and their parents or guardians, for those under 18) about the project and determine whether the patient meets study eligibility criteria.

Patients expressing interest in participating (and for those under 18 years old, their parents or guardians) will meet with the RA to discuss the study further and to be screened for eligibility. Screening for eligibility will include review of Mountain Manor treatment records to determine initial eligibility. Individuals who screen as eligible will be offered an initial informed consent, which will describe the risks and benefits of participation and will include information about alternative treatment options for those not interested in participating. Individuals meeting study criteria, as well as their parents for those under 18-years of age, will be told the following information regarding participation:

1) That they will have a baseline assessment that will last about 2 hours to ask about their history of drug and alcohol use, treatment and psychosocial functioning. The results of their history and physical examination, urine pregnancy, liver function, hepatitis and HIV tests that were conducted as part of their admission to treatment will be reviewed by the study physician and included as part of the research record to ensure that they meet eligibility requirements. During the course of the study, they can contact the MMTC medical staff 24-hours a day to discuss any concerns with their assigned medication. The RA will contact the project manager to obtain the participant's assignment to study condition through the use of a block randomization procedure in which, for each successive block of 4 participants within each gender, 2 will be assigned at random to the XR-NTX Condition and 2 will be assigned to TAU. Only the project manager and PI will have access to the random assignment table.

2) Those assigned to XR-NTX will, after achieving at least 6 days of abstinence from opiate use and having a spot urine test negative for opiates, will receive one low oral dose of naltrexone each of 3 consecutive days to test for opioid withdrawal. If the

patient is unable to stay for 3 days, then the oral doses of naltrexone will be administered over a 2 day period instead. (This option is deemed safer than discharging the patient before receiving the Vivitrol injection, which would put them at greater risk for relapse and possible overdose.) Those individuals who experience opioid withdrawal from the oral naltrexone will receive symptomatic medication for their withdrawal symptoms and will not receive the XR-NTX. Excluded individuals will be able to receive any other services available at the treatment center. Individuals who do not experience opioid withdrawal from the oral naltrexone will receive a monthly intramuscular injection of XR-NTX into alternating buttocks. The medication blocks the effects of opiates and each injection lasts approximately 4 weeks. The risks of the medication will be described (as outlined below). Participants will be told that XR-NTX is approved for use by individuals 17 years and older. 3) Those assigned to TAU will be able to receive whatever counseling and other services provided by MMTC that they would have received had they not participated in the study (except XR-NTX). These services might include buprenorphine as a dose taper or for a longer period of time, in keeping with their wishes (and the wishes of their parents, for patients under 18 years of age) and the recommendations of the treating physician and all the counseling and other services offered at MMTC.

4) All participants will be asked to return to either MMTC or the Friends Research Institute's office in Baltimore for follow-up interviews at 3 and 6 months after study entry for which they will be paid $30 per interview. At the 3-month follow up their liver function test will be repeated and at the 6 month follow-up their HIV and Hepatitis C test will be repeated. Liver function tests will also be repeated at months 1 and 6 for anyone receiving XR-naltrexone in the previous month. In addition, they will be asked to return to MMTC or the FRI office to leave a monthly urine sample and to be asked about any adverse events and their last menstrual period. Participants who receive the XR-naltrexone injection at month 6 will be interviewed at months 7 and 8 to be queried about adverse events. They will receive $20 for each of these interviews. Participants will also receive $20 for each visit at months 1, 2, 4 and 5. Participants who attend and complete follow-up visits in-person will have the opportunity to participate in a fishbowl type lottery drawing for the opportunity to win a range of prizes, with the maximum prize not to exceed $100 in value.

The study physician will meet with potential participants (and his/her parents, as appropriate) to review the treatment alternatives to participation, as well as the risks and benefits of participation. Alternative options to participation that are available at MMTC include a buprenorphine dose taper, buprenorphine maintenance or XR-NTX, all accompanied by counseling. In addition, methadone treatment is available by referral to outside agencies (although it is rarely desired by youth).

The informed consent process will include a consent quiz that will be re-administered up to three times until a score of 100% is achieved. Potential participants who are unable to score 100% on the consent quiz will not be eligible for participation. All participants will be informed that during the course of the study, they should report any concerns regarding study medication to the medical staff at MMTC through a 24-hour phone number.

As necessary, the consent process will be conducted by telephone with adults. In such cases the adult participant, parent or legally authorized representative, will receive a copy of the consent document(s) in advance so they can familiarize themselves with the consent form(s). The RA will then conduct the informed consent discussion by telephone, assuring adequate time to address questions, concerns, and to ensure adequate comprehension of the consent and the study information. Parents completing consent forms concerning their minor children's study participation will then complete an IRB approved consent quiz to verify comprehension. Parents completing the consent process regarding their own participation in the qualitative interviews will not complete a consent quiz. The signed and dated consent document(s) may be returned to the research staff by e-mail, facsimile or mail for the researcher's signature and date. This process will be completed before any research procedures begin.

6.3. Youth Participants in Qualitative Interviews

From the larger sample of 340 youth, purposive sampling will be used to select a sub-sample of 30 or more youth (approximately equal numbers from each Condition) to participate in semi-structured qualitative interviews and baseline, 3- and 6-months. Purposive sampling is a non-random process by which participants are selected in order to achieve a certain goal (i.e., to seek out a broad range of participants to insure that different view-points are represented). A diverse range of respondents will be selected with respect to age (approximately half from 15-19 age range), gender (approximately equal numbers of females and males), and drug of abuse (prescription opiates and other drugs). Youth who agree to participate in the qualitative interviews will be told that they will be asked questions about their treatment expectations, experiences and satisfaction with the medication (including social stigma and any side-effects experienced), views concerning dosing and other aspects of medical treatment, inclusion and utilization of psychosocial support services, current drug use, and issues related to treatment retention. Participants will be told that their involvement with the qualitative portion of the project will entail completing 3 oral interviews (at baseline, 3- and 6-month follow-up) that will be audio recorded, transcribed for accuracy, and that no identifying information will be linked with their interviews. Participants will be told that they will receive $30 for each interview that they complete.

6.4. Parent Participants in Qualitative Interviews

One parent or caregiver for each of the 30 or more youth participants in the qualitative interviews will be approached and invited to also participate in a series of 3 semi-structured qualitative interviews. Effort will be made to ensure participation from both mothers and fathers whenever possible, however, inclusion will also be based on the scope of their involvement in their child's life. Parents will be told that they will be asked questions about their treatment expectations for their child, satisfaction with the medication their child is receiving, views concerning dosing and other aspects of medical treatment, inclusion and utilization of psychosocial support services (including degree of family involvement in the treatment process), and issues related to treatment retention. Parent participants will be told that their involvement will entail completing 3 oral interviews (at baseline, 3- and 6-month follow-up) that will be audio recorded, transcribed for accuracy, and that no identifying information will be linked with their

interviews. Parent participants will be told that they will receive $30 for each interview that they complete.

6.5. Baseline Medical Screening

As is standard practice upon admission to the treatment center, MMTC staff will conduct a history and physical exam which includes a neurological and psychiatric assessment, as well as an assessment for coagulopathy (e.g., hemophilia by family history). In addition, staff will draw blood to test liver function and for hepatitis C and for HIV infection and a urine sample for pregnancy testing. The study physician will review the physical exam and laboratory test results for inclusion/exclusion criteria of those individuals who provided informed consent to participate. Individuals excluded for medical or psychiatric reasons will be provided appropriate treatment or referral for follow-up to treat the reason for exclusion. Individuals who meet inclusion criteria will receive study assessments described below, be randomly assigned to XR-NTX or TAU, and receive treatment at MMTC.

6.6. Research information

The following instruments will be administered at baseline, 3- and 6-month follow-up to study participants: *Self-reported opioid and other drug and alcohol use (Time Line Follow Back)* used in the CTN 0010 study;[7] *Criminal Activities* using time line follow back techniques and drawn from the Friends Research Institute's supplemental questionnaire;[76,77] *CIDI-2 Substance Abuse Module* to determine whether individuals met the DSM-5 criteria for opioid use disorder during the one month period prior to their baseline and 3- and 6- month follow-up assessments;[81,78] *Risk Assessment Battery* (RAB) a brief questionnaire covering substance use and sexual HIV risk behaviors that has been extensively used with drug dependent populations, including youth;[83,82] *Short Form-12* (SF-12) a widely used brief instrument designed to measure physical and mental health status;[84,85] *Economic Form 90*, a self-administered survey will be modified to collect data on economic outcomes before, during, and after treatment; *EMIT urine drug testing* for opioids, marijuana, cocaine and benzodiazepines at baseline and monthly thereafter; *HIV Testing* at baseline and 6 months testing will be conducted by a certified laboratory on blood samples drawn by MMTC staff. The samples will be screened for HIV 1 and 2 via ELISA and confirmed with Western Blot. Participants will have pre- and post-test HIV counseling. All study instruments, interviews and tests are described in detail in the Methods Section of the Protocol (see Measures above) and have been administered successfully quite widely as part of drug abuse research studies, including in studies of youth.

6.7. Youth and Parent Qualitative Interviews

The semi-structured qualitative interviews for both youth and their parents will cover the following content domains: treatment expectations, experiences and satisfaction with the medication (including social stigma and any side-effects experienced), views concerning dosing and other aspects of medical treatment, inclusion and utilization of psychosocial support services, current drug use, and issues related to treatment retention. The interview content for youth and their parents/caregivers will overlap considerably, so as to provide an opportunity for a direct comparison of stakeholder perspectives.

6.8. Random Assignment

Individuals wishing to participate will be administered a brief informed consent quiz to ensure they understand the risks and benefits of participation. After providing informed consent and administering the study assessments, the RA will contact the project manager to obtain the participant's assignment to study condition through the use of a block randomization procedure in which, for each successive block of 4 participants within each gender, 2 will be assigned at random to the XR-NTX Condition and 2 will be assigned to TAU. Only the project manager and PI will have access to the random assignment table.

6.9. Safety data

We will collect the following safety data:

Medical history and physical exam. Personal medical and psychiatric history will be collected as part of the clinic's usual MMTC intake procedure and reviewed by the study physician to determine eligibility for participation. A physical exam, which includes a neurologic exam and neuropsychiatric mental status evaluation, will be conducted. A history of coagulopathy (e.g., hemophilia) will be obtained.

Specimens. At baseline and 3 month follow-up, liver function tests (AST and ALT) will be conducted for all participants. In addition, participants assigned to XR-naltrexone and anyone who received XR-Naltrexone in the previous month will have repeat AST and ALT at 1- and 6-month post-baseline. Individuals with liver function tests four times normal or greater will not receive XR-NTX and will be referred to alternative treatments at MMTC or elsewhere. Such individuals will be referred to medical follow-up to their primary care physician. A urine pregnancy test will be taken at baseline and at follow-up for female participants (as indicated).

Adverse Event Check. On a monthly basis, all participants will complete an adverse event form and complete the Beck Depression Inventory (BDI-II), a 21-item self-report questionnaire. Depressed participants will have a psychiatric evaluation on site by the Co-I or another mental health staff member of MMTC. Females will be asked about their last menstrual period (and have a urine pregnancy test, monthly) and those receiving XR-NTX will have their injection site examined prior to each XR-NTX injection. Participants who receive the XR-naltrexone injection at month 6 will be followed for an adverse event check-in at months 7 and 8. Serious adverse events will include hospitalizations, birth-defects, and deaths and will be reported as described below.

6.10. Reporting of All Adverse Events

Potential risks

All study participants, regardless of random assignment, may be exposed to risks associated with confidentiality and emotional discomfort as the result of instrument administration (as described below) and participation in qualitative interviews.

Confidentiality. Participants will be asked to provide information regarding a number of sensitive behaviors (e.g., drug use, sexual behaviors, and illegal activities). The inappropriate release of such confidential information could result in loss of

employment, arrest, family or social problems. Careful steps to minimize such risks will be taken as described below.

Emotional discomfort. There is a small chance that participants may become upset when discussing their history of drug use or sexual behavior. This is an extremely rare event and steps will be taken to minimize and address this risk as described below.

Risks associated with TAU. Other than the risks of loss of confidentiality and emotional discomfort (as described above), there are no additional risks associated with random assignment to TAU. All study participants, regardless of random assignment, will be told that continued or renewed opioid use can lead to medical problems including infections such as HIV, hepatitis and soft-tissue infections (for those who inject drugs) and overdose death (particularly for those individuals who are not receiving opioid agonist treatments of buprenorphine or methadone).

Risks associated with XR-NTX. Prior to random assignment, participants may experience short-lived opioid withdrawal symptoms provoked by oral naltrexone. We anticipate that this will be uncommon as only patients who report not using opioids for at least 6 days and have a spot urine opioid negative drug test will be given oral naltrexone. Participants who do not experience opioid withdrawal from oral naltrexone and who are randomly assigned to and receive XR-NTX may experience one or more of the following side effects:

1. Injection site reactions including tenderness, hardening, swelling, redness, bruising or itching. In rare cases, it may be necessary to treat a severe site reaction with surgical debridement which may leave scarring.
2. Opioid withdrawal symptoms. Despite having no opioid withdrawal symptoms to the oral naltrexone, it is possible that participants might experience nausea or other opioid withdrawal symptoms.
3. Naltrexone in excessive oral doses has been reported to cause increased liver enzymes. XR-NTX does not appear to be a hepatoxic at the recommended doses.
4. Participants in both groups carry the risk of relapse to opioid dependence. Relapse to opioid use after discontinuing naltrexone carries a risk of opioid overdose and death since tolerance after a period of abstinence is low. Participants (and their parents) will be informed of these risks and of treatment alternatives, including methadone or buprenorphine maintenance.
5. Naltrexone injections will block the effects of opioid analgesics. Participants (and their parents or guardians, as age appropriate) will be given a card describing XR-NTX to medical staff in case of emergency need for opioid analgesia. General anesthetics, nerve blocks and non-steroidal pain medications are not affected by naltrexone and can be used to manage acute pain.
6. Allergic reactions. During clinical trials with XR-NXT there was one case and one suspected case of eosinophilic pneumonia that resolved with antibiotics and steroids. Other allergic reactions are possible and include rash, itching or facial swelling.

7. Depression and suicidal ideation. The 21-item BDI, which has been used extensively, including among youth, will be repeated monthly at the same time as urine collection for drug testing to screen for depression and suicidal ideation. Participants and their parents will be informed about this possible side effect and will be told to contact the study staff and to seek medical care should this occur.

6.11. Potential Risks for Parent Participants

Confidentiality. Parent participants will be asked to provide information regarding their child's behaviors, including sensitive issues such as drug use and possible illegal activities. The inappropriate release of such confidential information could result in family or social problems. Careful steps to minimize such risks will be taken as described below.

Emotional discomfort. There is a small chance that parent participants may become upset when discussing their child's history of drug use. This is an extremely rare event and steps will be taken to minimize and address this risk as described below.

6.12. Protection against Risks

Risk Associated with Confidentiality. To protect against loss of confidentiality, we have: (1) obtained a Federal Certificate of Confidentiality to protect against the release of confidential information; (2) provide all staff with training on their responsibilities for maintaining participant confidentiality; (3) use unique identifiers for participant information in the database; (4) keep all data 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 Pennsylvania Data Management Unit which has double password protection on its server and files. All data (quantitative and qualitative) transmitted 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 Associated with Emotional Discomfort. All instruments to be employed have been used frequently and without incident with drug abusers. RAs will be trained to be alert to indication of participant discomfort and will discontinue administration of research instruments if a study participant shows discomfort. If necessary, the Co-Investigators are psychiatrists and they will work with the participant to alleviate this discomfort.

Risk Associated with Oral Naltrexone. Participants assigned to XR-NTX will have their absence of recent opioid use confirmed via a urine drug test for opioids (including oxycontin), methadone and buprenorphine. A low dose of oral naltrexone will be given to those with negative urine opioid tests who report not using opioids in the last 6 days to further reduce the risk of opioid withdrawal from XR-NTX and to reduce the likelihood that the participant is allergic to naltrexone. Any reaction to oral naltrexone will be relatively short-lived (several hours) and will be treated symptomatically by the study physician.

Risks Associated with XR-NTX.

1. Opioid withdrawal. Should opioid withdrawal occur following XR-NTX administration, the study physician will treat the participant symptomatically.

2. Injection site reactions. Injection site reactions will be treated symptomatically. In rare cases, a surgical consult will be obtained for severe site reaction to determine if surgical debridement is necessary.
3. Liver function elevations. Baseline liver function tests will be used to exclude individuals with four times normal AST or ALT levels. Should repeat liver function tests at 1-, 3-, or 6- months post-enrollment show four times normal values for AST or ALT, XR-NTX will be discontinued. Liver function tests will be measured for participants in both study Conditions to provide additional safety data regarding XR-NTX in this population. Participants with elevated liver function tests will be referred to their primary care physicians for follow-up.
4. Relapse to opioid use. Participants in both groups will receive information regarding the risk of overdose and will be enrolled in drug abuse counseling. XR-NTX, if taken as indicated, blocks the effects of opioids and will protect against overdose.
5. Pain. Naltrexone injections will block the effects of opioid analgesics. Participants will be given a card describing XR-NTX to medical staff in case of emergency need for opioid analgesia with the number of the study physician for consultation, if needed. General anesthetics, nerve blocks and non-steroidal pain medications are not affected by naltrexone and can be used to manage acute pain.
6. Allergic reactions. The administration of a shorter acting oral naltrexone will help to screen for allergies to NTX prior to the administration of XR-NTX. Participants will be told about allergic reactions and to call the study physician or to go the nearest ER should they experience allergic reactions, which will be treated symptomatically with benadryl and/or steroids as appropriate.
7. Use during pregnancy. Naltrexone is not approved for use during pregnancy. A urine pregnancy test for female participants will be administered prior to admission to treatment. Female participants on medication will be asked monthly about their last menstrual period and a pregnancy test will be repeated monthly. In the event a study participant becomes pregnant, the participant will need to meet with their medical provider to determine whether or not to discontinue XR-NTX and study staff will follow the participant to gather pregnancy outcome information.
8. Depression and Suicidal Ideation, and Attempts. People with opioid addiction, including those taking XR-naltrexone, can experience depression, suicidal thinking, and suicide attempts. It is possible that participants might become sad or depressed during the study. Participants will be told to call the study staff or seek help in the nearest emergency room if they have thoughts about hurting or killing themselves.

1.1. Risk/Benefit Ratio

Every effort will be made to minimize the risks to participants in this study. Exclusion criteria, voluntary participation, protection of confidentiality will help minimize risk to subjects. With regard to study benefits, all participants will receive drug abuse treatment and those assigned to XR-NTX will receive this medication which has been

shown to reduce opioid use and is approved by the FDA for the prevention of relapse to opioid dependence in individuals 17 years of age and older. Half of the participants will receive treatment as usual and hence will assume no additional risk for study participation other than loss of confidentiality or emotional discomfort from research interviews. Results from this study may help determine the utility of using XR-NTX for youth in preventing opioid use and relapse to opioid dependence. Considering the potential therapeutic and scientific benefits and the risk to the subjects, the risk-benefit ratio appears within acceptable limits.

1.2. Importance of the Knowledge to be Gained

While opioid dependence is a large and growing problem among youth, there are little data available on the effectiveness of the use of recently approved XR-NTX in this patient population. Given the substantial relapse rate among treated individuals, and the risks associated with opioid use, studying XR-NTX is of considerable importance to the field and to public health.

2. DATA AND SAFETY MONITORING PLAN

Responsibility for Safety Oversight. The Principal Investigator and her study staff, the FRI Institutional Review Board (IRB), and the FRI Data Safety Monitoring Board (DSMB) will provide safety oversight for the project. In addition, an external medical safety monitor (an independent physician with expertise in naltrexone therapy and heroin addiction) will report her review of adverse events to the PI, the project's medical staff, and the FRI's IRB. She will review reports on the study and be informed by the PI of any information that has bearing on the safety of the participants. The PI will be responsible for conducting a literature search on XR-NTX no less frequently than every six months to identify any emerging research findings that might influence study procedures. Finally, the PI and external medical safety monitor will stay alert to any changes in the FDA labeling of XR-NTX.

Report of Safety-Relevant Information to NIDA. The Principal Investigator is responsible for informing NIDA of any safety-relevant actions taken by the FRI's Institutional Review Board as a result of its 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 participant 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 participate.

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 the FRI's IRB 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 the FRI's IRB and the NIDA Program Official.

Quality Control of Data. RAs 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. Data processing staff will review CRF's the next day. The Project Manager will be advised of any forms needing correction, and he/she will bring these to the attention of the interviewer. 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.

2.1. Data and Safety Monitoring Board (DSMB)

The FRI DSMB, consisting of outside experts in clinical trials, the treatment of opioid dependence and biostatistics, will review the progress of the study and monitor participant intake, outcomes, adverse events and other safety related matters. The DSMB will meet at the start of study enrollment, six months into recruitment, and every year thereafter. The DSMB will review all SAEs. The project's statistician will perform interim analyses, at times determined 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 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.

2.2. Criteria for Suspending or Terminating the Study

The study may be modified, suspended, or terminated at the recommendation of the PI, DSMB, or by the FRI IRB in the interests of protecting study participants. The PI, medical safety monitor, DSMB and/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 decision to stop the study with regard to safety/adverse event considerations are based on the number and severity of study-related adverse events, particularly those determined to be fatal or of high severity. The study may also be terminated if the DSMB decides that there has been an emergence of an unexpected serious adverse event or events.

Termination Due to Favorable Benefit-Risk Ratio. If the DSMB determines it appropriate to conduct an interim analysis and it provides compelling evidence for superiority of one of the other study Conditions, 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 DSMB requires an interim efficacy analysis and its 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; serious 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 decision in consideration with other relevant information regarding the trial.

2.3. Reporting of Serious Adverse Events

Participants will be informed that during the course of the study, they should report any concerns regarding study medication and experienced adverse events to the medical staff at MMTC through a 24-hour phone number. Each Adverse Event will be classified by the PI as serious or non-serious and appropriate reporting procedures followed. Serious Adverse Events are defined as any death; life-threatening event; any permanent or substantially disabling event; any event that requires or prolongs inpatient hospitalization; or any congenital anomaly. This category also includes any other important medical event that a study investigator judges to be serious because it may jeopardize the participant or require intervention to prevent one of the above reportable outcomes, or which would suggest a significant hazard, contraindication, side effect, or precaution. An Unexpected Event is one that is not described with respect to nature, severity, or frequency in the current protocol, or XR-NTX's FDA-approved product labeling.

The PI will promptly report all Unexpected, Serious Adverse Events to the Friends IRB and NIDA. Unexpected, Serious AEs that occur will be reported through FDA's MedWatch program (http://www.fda.gov/medwatch/index.html). As required, expedited reporting of Serious Adverse Events to NIDA will adhere to the following guidelines:

a) Apply regardless of the investigator's assessment of the relatedness of the Serious Adverse Event to the intervention under study.

b) Apply equally whether the FDA will require an IND or not.

c) Apply to any Serious Adverse Events that occur during the post-treatment observation period defined by the protocol.

d) Apply to suicidal or homicidal behavior that causes a Serious Adverse Event in the subject or someone else (e.g., hospitalization or death).

Any Unexpected, Serious Adverse Events which occur during the course of this investigation and follow-up period, whether or not related to the study protocol, will be reported within 24 hours by telephone to NIDA (NIDA program official TBN) and the FRI IRB. The telephone report will be followed within 2 days by sending a completed Serious Adverse Event Form with demographic information and a narrative explanation of the event. The narrative will also provide details of relevant screening measures, medical history & physical, treatment compliance, participant reports of Serious Adverse Events and any other information the Principal Investigator deems appropriate.

Attached to the Serious Adverse Event Form will be photocopies of relevant source documents (Case Report Forms). The Principal Investigator will address whether there is a need to amend the protocol, and/or to inform current and future participants of a change in description of risk, either in the consent form and protocol, or by other written or verbal communication. The written Serious Adverse Event report will also be sent to the FRI Institutional Review Board.

2.4. Reporting of All Adverse Events

All Adverse Events occurring during the course of the study will be collected, documented, and reported by the Principal Investigator according to the specific procedures detailed below. An Adverse Event is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial, whether or not the event is considered medication-related. A new illness, symptom, unfavorable and unintended sign, or worsening of a pre-existing condition or abnormality is considered an Adverse Event. Stable chronic conditions that are present prior to clinical trial entry and do not worsen are not considered Adverse Events. For this study, Adverse Events will include symptoms reported by the patient and abnormal measures of clinical importance noted by study staff.

Adverse Events will be assessed according to the procedures specified in the protocol. Additionally, study staff will assess patients for any medical or psychiatric side effects by asking the participant “How have you been feeling since I saw you last?” Study staff will also review the previous Adverse Event (AE) Form and inquire whether any of those events are continuing. In addition, the AE Form will be administered (by telephone, if necessary) at 4 and 8 weeks after their 6-month injection (i.e., at months 7 and 8 post-baseline) for those participants who elect to receive an XR-naltrexone injection at month 6. Study investigators will follow all Adverse Events, regardless of severity, until resolved or until 8 weeks following completion of treatment. Each new or unresolved Adverse Event will be recorded on the Adverse Event Case Report Form with a brief verbatim ‘title’, a severity ranking, and any additional description, according to the procedures (see below). If an Adverse Event is reported that requires medical attention, it will be reported to the study physician immediately and forwarded for PI review. The study physician will review the AEs weekly to assess their possible relationship to study medications.

A summary report of all Adverse Events will be prepared annually to be submitted to the IRB, DSMB, FDA and NIDA. The analysis of all adverse events accumulated-to date will include a list of all Adverse Events. Participants’ descriptions of adverse events from AE Forms will be reasonably grouped, counted, and compared by treatment groups. A designation of ‘more-common and drug-related’ will be given to events occurring at an incidence of least 5% in subjects assigned to either condition. Other significant (non-serious) adverse events that will be reported include: marked abnormalities in liver function tests or other laboratory tests; adverse events leading to dropouts; and adverse events that lead to the addition of concomitant therapy. The summary report of all adverse events will be provided to NIDA at the time of the study’s continuing IRB reviews.

2.5. Inclusion of Children

All 340 study participants will be between the ages of 15 and 21. Children in this age range are the focus of the study because there is a need to improve their drug abuse treatment outcomes and extended release naltrexone has been little studied in this patient population. Participants 15-17 years of age will be asked to provide assent and their parents or guardians will be asked to provide informed consent. Those 18 years and older will be asked to provide informed consent. The treatment team and study site are highly experienced in providing opioid dependence treatment for youth 15-21 years of age in their specialized treatment unit.

2.6. Inclusion of Women and Minorities

Participation of Women. Considering characteristics of new admissions to Mountain Manor Treatment Center in 2010, sufficient numbers of women will be represented in the participant population. It is estimated that of the 340 participants, 136 (40%) will be women. A number of our publications have focused on gender differences with regard to drug use and patient outcomes.

Participation of Minorities. Considering characteristics of new admissions to Mountain Manor Treatment Center in 2010, we expect that the participation of minorities in the proposed study will mirror that of the program's new admission in 2010. Thus, we estimated that of the 340 participants, 24 (7%) will be African-American and 316 (93%) will be White and 10 (3.4%) will be Hispanic. We have been working with opioid-dependent individuals, both African-American and White in Baltimore since the mid-1960s and have acquired an understanding and awareness of the social and cultural factors that operate within these populations. The population of Hispanics in Baltimore City is very small (i.e., just over 4% of the population) and few are represented among the patients in its drug treatment programs. Hence, we do not anticipate having the ability to recruit a significant number of Hispanic participants. Many of our publications have focused on the differences between African-American and White opioid-addicted individuals with regard to the natural history of drug addiction, lifestyles, and attitudes toward opioid addiction and its treatment.

3. FACILITIES AND RESOURCES

3.1. Office: Friends Research Institute, Inc.

Friends Research Institute (FRI) is located in offices on the first level of 1040 Park Avenue, Suite 103 in Baltimore, MD., zip code 21201 (8,695 sq. ft.). The space is completely equipped for this project, including areas set aside for conducting interviews with research participants. The facilities are ADA compliant and easily accessible via public transportation (bus and/or light rail). FRI offices are available 5 days a week. The FRI office in Baltimore, where the investigators will be located, is within 20 minutes of Mountain Manor Treatment Center.

Research Environment. FRI's Baltimore office was established in the mid 1960s to create a supportive research environment for the interdisciplinary work of behavioral scientists who have conducted prevention and intervention research in drug abuse treatment. Currently, investigators at FRI in Baltimore are undertaking a diverse program of prevention and intervention research including the following NIDA-funded

studies; 1) Entry into Comprehensive Methadone Treatment via Interim Maintenance; 2) Buprenorphine for Prisoners; 3) Criminal Justice Drug Abuse Treatment Study (CJ-DATS); 4) Intensive Outpatient v. Outpatient Treatment among African American Buprenorphine Patients; 5) SBIRT in New Mexico; 6) Naltrexone for Probationers; 7) Re-engineering Methadone Treatment; 8) Mid-Atlantic Node of the Clinical Trials Network; and 9) Seek, Test, and Treat: HIV in the Criminal Justice System. Dr. Frank Vocci, a pharmacologist and former Director of NIDA Medication's Development Division, became the President of FRI in January, 2009 joining FRI's seasoned investigators.

FRI investigators have also created and fostered lengthy tenured relationships with federal, state, and local agencies. More importantly FRI has become engrained in the fiber of Baltimore City, collaborating with the Baltimore City Substance Abuse Authority and the Single State Agency as well as a multitude of treatment agencies and the Department of Corrections to successfully produce research that benefits the lives of many Baltimore City residents who have been drug-dependent, and their families. FRI has a long-standing research collaboration with Co-I Fishman and Mountain Manor Treatment Center (described below) and is currently conducting an R01 studying extended release naltrexone for adult probationers and is collaborating as part of the Mid-Atlantic Node of the CTN.

Institute Organizational and Research Infrastructure. The administration of the FRI Center is supported through the coordinated efforts of an experienced and capable resource team charged with meeting the operational needs of its investigators and collaborators. The infrastructure for these efforts consists of three key elements: 1) Secretarial Services; 2) Computer Support; and 3) Website and ListServ functionality.

FRI currently has in place a research support infrastructure readily adaptable to meet the needs of field research. This infrastructure is composed of four units: 1) Data Acquisition; 2) Data Management; 3) Quality Assurance; and 4) Statistical Services. While functionally separate, these four units are in continuing communication with each other, with supervisory FRI researchers, and the University of Pennsylvania Data Management Unit dynamically managing all issues related to research support, from study design through statistical analysis, interpretation, and publication under the direction of the investigators.

3.2. Clinical: Mountain Manor Treatment Center

The Mountain Manor Treatment Center is located at 3800 Frederick Avenue, Baltimore, MD 21229.

The Center is a Joint Commission on Accreditation of Healthcare Organizations (JCAHO)-accredited substance abuse treatment provider. Mountain Manor staff include physicians, 24-hr nursing, and nurse practitioners. This site has a young adult 15 bed residential program and an adolescent/young adult outpatient continuum of care (including PHP, IOP, OP, mental health clinic). The program admits approximately 6 youth per week ages 17-21 for the treatment of opioid withdrawal symptoms, who could be eligible for the study.

Under the leadership of Co-I Marc Fishman MD, study physician, Mountain Manor's Medical Director and member of the psychiatry faculty at the Johns Hopkins University School of Medicine (JHUSOM), Mountain Manor has a long and established history of academic partnerships and conducting research with Friends Research investigators. Mountain Manor is designated as a community treatment provider in the Mid-Atlantic Node of the National Institute on Drug Abuse (NIDA) Clinical Trials Network (CTN), whose Co-PI is the present study's Co-I Schwartz. Mountain Manor served as one of the sites for the CTN Adolescent Buprenorphine Protocol (CTN-0010), and in fact recruited the most participants (opioid-dependent adolescents and young adults) of any of the sites. Mountain Manor investigators also conducted a CTN ancillary study examining co-morbid psychiatric disorders in adolescent opioid users. Mountain Manor was one of the sites for the CTN study of OROS-methylphenidate (Concerta) for adolescents with substance abuse and ADHD. Importantly it is also a site in the Friends Research Institute's R01 to study naltrexone in adult probationers.

Mountain Manor has been the site of several CSAT-funded programs with Dr. Fishman as PI, including: the Adolescent Treatment Models (ATM) project, which documented program models and evaluated 12-month outcomes for 11 promising community treatment providers nationally; a Targeted Capacity Expansion (TCE) project that established an integrated psychiatric/mental health clinic for adolescents in outpatient substance abuse treatment; an Adolescent Residential Treatment (ART) project implementing assertive continuing care following adolescent residential treatment; and a current Targeted Capacity Expansion (TCE) project implementing school-based substance abuse MET/CBT counseling.

Mountain Manor Treatment Center serves as a training site for the addiction rotation for Johns Hopkins Child Psychiatry fellows, for research and clinical electives for the Hopkins General Psychiatry residents, for the adolescent rotation for University of Maryland Addiction Psychiatry fellows, and for Johns Hopkins Pediatric residents during their adolescent medicine rotations.