Buprenorphine group medical visits for drug users at risk for HIV

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NCT02526212

Last Reviewed February 16, 2018

Study Protocol

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I. Overview and specific aims:

The primary goal of this research is to improve the effectiveness of buprenorphine maintenance treatment (BMT) within primary care. In the United States, opioid overdose deaths have tripled over the past decade (reaching at least 17,000 in 2010) and continue to increase at alarming rates.[1-3] Integrating BMT into primary care has increased access to opioid addiction treatment by partially addressing barriers such as stigma, limited access, and health system fragmentation;[4-7] however, BMT outcomes have yet to be optimized in primary care.

For BMT patients with persistent opioid abuse despite medical management, the ideal approach to treatment intensification within primary care is unknown. Typically, recommendations include increasing frequency of visits and referring for psychosocial counseling, but physicians already cite time pressure and difficulties referring to counseling as challenges to providing BMT.[13-15] Instead, integrating intensive behavioral interventions into primary care could improve BMT outcomes without requiring a referral to specialists. Group medical visits are a promising way to achieve this goal without straining primary care practices.

We propose that providing BMT as part of a group medical visit will improve treatment outcomes for patients with persistent opioid abuse, because members become accountable the group, are exposed to beneficial habits of others (i.e. positive deviance), and can receive efficacious behavioral interventions concomitantly with medical management.[21-23] Group medical visits, which provide disease-specific education, instruction on self-management skills, peer support, and individualized medical management, are increasingly utilized to improve outcomes in chronic medical conditions with strong behavioral components (e.g., diabetes and depression).[24,25] Group medical visits deliver team-based care to multiple patients simultaneously, which can improve efficiency in patient-centered medical homes and other primary care settings.[29,30]

We have developed a preliminary model of BMT group medical visits, conducted focus groups with BMT patients and providers, and we will use this data to develop a manualized group-based BMT intervention (G-BMT). We will then conduct an RCT of the G-BMT intervention within primary care to preliminarily test its efficacy, acceptability, and feasibility. Participants who have persistent opioid abuse while receiving BMT in primary care will be randomized to the G-BMT intervention (40 participants in 5 groups) or to intensify BMT (treatment as usual) with their individual primary care physician (40 participants). The specific aims for this developmental study include:

Aim 1: To develop the G-BMT intervention for primary care

We will adapt a preliminary model of BMT group medical visits to meet the needs of opioid users with persistent opioid abuse.

Aim 2: To pilot test G-BMT for efficacy, acceptability, and feasibility in an RCT within primary care H1: In a 16-week RCT of G-BMT, participants who receive the G-BMT intervention (vs. treatment as usual) will have higher abstinence rates (primary outcome, efficacy), fewer HIV risk behaviors (efficacy), and greater satisfaction with treatment (acceptability) and adherence to medical visits (feasibility).

II. Background and Significance

In 2010, drug overdose replaced motor vehicle accidents as the leading cause of accidental death in the United States.[34] This epidemic has primarily been driven by opioid addiction, with opioid analgesic use, misuse, and overdose tripling between 1999 and 2010.[1] Opioid analgesic overdose deaths reached nearly 17,000 in 2010, the latest year that data is available, while heroin overdoses likely cause an additional 2,000 deaths annually.[3,35] As regulations regarding opioid analgesic prescribing have become more restrictive, heroin use and overdose have also seen increases. In New York City, between 2011 and 2012, opioid analgesic overdose deaths decreased by 12%, while between 2010 and 2012, heroin overdose deaths increased by 71% and remain the leading cause of drug overdose death.[36] In the United States, opioid addiction is a public health crisis with its epicenter in New York City.

Buprenorphine maintenance treatment (BMT) is an essential component of opioid addiction treatment. Of the 2.3 million Americans in need of opioid addiction treatment in 2010, less than 20% were admitted to opioid addiction treatment facilities, leaving a large treatment gap.[37,38] Because of the flexibility of regulations, BMT has the capability of addressing this treatment gap and has now surpassed methadone maintenance in the number of patients treated annually.[39] BMT effectively reduces opioid abuse and has been successfully integrated into HIV and primary care settings.[12,40,41] The main limitation to BMT in primary care is that it is low intensity treatment and many patients continue to abuse opioids. In primary care, retention rates of 59-93% and opioid abstinence rates of 43-76% have been reported over 10-24 weeks,[10,43-47] leaving approximately half of BMT patients in need of more intensive treatment interventions.

Intensification of treatment can be challenging in primary care. If BMT patients do not achieve abstinence with medical management alone, there is no evidence-based approach to intensifying treatment. Referring for additional psychosocial counseling can be challenging.[48-50] The following algorithm is often used for treatment decisions following BMT induction in primary care: 1. Patients achieving prolonged abstinence enter a maintenance phase of treatment and typically follow-up for monthly visits; 2. *Treatment Intensification*: if patients continue to abuse opioids, visit frequency is increased to twice monthly or weekly, patients are referred for psychosocial counseling, and medication dosage may be increased; 3. *Referral*: with persistent opioid abuse following intensification, referral to a methadone maintenance treatment program or addiction specialist is usually

recommended.

In clinical practice, though, there are barriers to following these steps. Insurance coverage, costs, and provider availability limit referral for psychosocial counseling, and patients may be reluctant to transfer their care to addiction specialists or change from buprenorphine to methadone. Increasing visit frequency may be impractical for busy primary care physicians with large patient panels. Additionally, whether increasing treatment intensity improves outcomes in unknown. Ultimately, when BMT patients fail to reach goals of abstinence with medical management alone, many drop out of care or their providers terminate BMT. An option for treatment intensification within primary care will fill in an important gap in care, but data are needed to determine whether this results in improved health outcomes.

Group medical visits are a promising model for delivery of multi-disciplinary care for chronic medical conditions. In developing the G-BMT intervention, we will use the model of group (or shared) medical visits, which has been increasingly utilized in primary care, and provides a compelling number of advantages to individual-based care. Adapting BMT to this model will allow for integration of behavioral interventions and medical management, which will make increased visit frequency feasible and minimize the need for referral to psychosocial counseling. Group medical visits emphasize multidisciplinary and patient-centered care, and have had greatest benefit in management of diabetes, depression, and other chronic conditions with strong behavioral components.[29,30] During group medical visits, provider teams simultaneously care for multiple patients and deliver disease-specific education, instruction on self-management skills, and individualized medical management. Group medical visits are associated with improved adherence, decreased health care utilization (outpatient and hospitalization), improved access to care, increased self-efficacy, and improved clinical outcomes when compared with usual care.[24,25,65-73] This model of care is promising for addiction treatment, and has been implemented for other chronic conditions, but group medical visits have yet to be studied for BMT.

III. Research Design & Method

Overview: We will conduct a 16-week RCT in primary care to preliminarily test the G-BMT intervention (8 weekly group visits) for efficacy, acceptability, and feasibility in comparison to treatment as usual (TAU) among BMT patients with persistent opioid abuse. Eighty participants with ongoing opioid abuse in office- based BMT will receive treatment intensification in the G-BMT intervention or receive TAU. We will test **efficacy** by collecting interview, urine, and medical record data examining *abstinence* (primary outcome), *retention in treatment*, and *HIV-risk behaviors*, including drug-related and sexually-related risk factors. We will test **acceptability** by assessing patient and provider satisfaction following the trial. We will test **feasibility** by examining process measures, such as *medication and visit adherence* and fidelity to the intervention manual.

Setting: The G-BMT intervention will be implemented at a single Montefiore community health center (CHC) that

offers primary and specialty care to over 15,000 adult patients. The CHC is representative of those serving low-income urban neighborhoods; over 65% of patients have public insurance and most live in the surrounding neighborhoods of the South Bronx, which are 57% Hispanic and 39% Non-Hispanic Black, and remain devastated by drug use and HIV/AIDS.[91] The CHC has provided BMT to more than 700 patients since 2006, and has been used extensively for BMT-related clinical research.

Study Participants: *Eligibility Criteria:* 1) Currently receiving BMT at the CHC; 2) Received BMT for ≥ 12 weeks; 3) Persistent opioid abuse (urine drug testing positive for an unprescribed opioid in the previous 6 months or self-reported drug use in the previous 6 months); 4) ≥18 years old; 5) fluent in English or Spanish. *Exclusions:* 1) Contraindications to BMT (alcohol use disorder; benzodiazepine use disorder; unstable mental health condition); 2) Pregnancy; 3) Unwillingness to participate in group-based BMT.

Recruitment: We will review a register of BMT patients at the CHC who have consented to be contacted about research studies. We will contact patients who meet inclusion criteria and their providers. We will also extract data quarterly from electronic medical records to identify patients who have started buprenorphine treatment within the last 12 weeks. We will not contact patients directly, but instead, we will contact their primary care providers who will inform patients about the study and give the research team permission to contact patients. We will send potential participants letters from their PCP inviting them to participate in the study. Fliers describing the study will be posted at the CHC. The study will be described at staff meetings.

Randomization: A research assistant will contact and meet with eligible patients at the CHC to describe the study. At enrollment, written informed consent will be obtained, and forms to release medical records will be signed. Randomization will occur in blocks of 16 via a sealed envelope with allocation (G-BMT vs. TAU).

Screening Procedures: Potential participants who contact the study coordinator will be screened for inclusion and exclusion criteria. The study coordinator will also call potential study participants who are identified by PCPs or on the BMT register. The study coordinator will administer a three part screener by phone or in person. For patients referred to the study by their PCP, the study coordinator will check records to confirm: receipt of BMT for ≥ 12 weeks and documentation of illicit opioid use in the prior 6 months. The study coordinator will elicit oral informed consent based on a standard script and then ask seven screening questions to confirm receipt of buprenorphine, ongoing illicit opioid use, interest in group treatment, pregnancy, and other study inclusion/exclusion criteria. We will not be conducting pregnancy tests. To screen for unstable mental health conditions, the research coordinator will administer the suicidality, PTSD/violence risk, and psychosis modules from the MINI 6.0. If criteria for any of these conditions are met or if the research coordinator expresses concerns about group suitability, Dr. Fox will make a clinical assessment in person prior to study enrollment.

Research Visits: The research assistant will meet with all participants at enrollment and at 2, 4, 6, 8, 12, and 16 weeks

following initiation of G-BMT or TAU. Research visits, which are separate from group medical visits or individual provider visits, will occur in a private room at the CHC and participants will receive $25 compensation following completion of research activities. At each visit, computerized interviews and urine will be collected. Six months after enrollment, medical record data will be extracted for additional data collection.

Clinical Visits:

G-BMT intervention: The G-BMT intervention will begin with 8 weekly 90-minute group medical visits after a block of 8 participants has been randomized to the intervention arm. The anticipated protocol for G-BMT is described below. Urine drug tests will be collected at each group visit and will be used as a secondary study outcome and to modify management of addiction treatment as described.

The G-BMT intervention will include group medical visits where 8-10 patients simultaneously receive care from a multidisciplinary team of a generalist physician and a behavioral specialist (i.e. clinical social worker or psychologist). Patients will be expected to attend each 90 minute session, sign a confidentiality agreement, and will receive BMT prescriptions (one week supplies) only at the end of sessions (not in between visits). We anticipate that the G-BMT intervention will include: 1) BMT-related education, 2) instruction on self- management skills, 3) peer support, and 4) individual medical management.

Buprenorphine-related education: Topics will include buprenorphine pharmacology, neuroanatomic changes that occur with addiction, HIV risk reduction, and other topics related to opioid addiction. The generalist physician will deliver 15 minutes of information per visit.

Self-management skills: Empowering participants for self-management of their addiction will occur through an adapted cognitive behavioral intervention. Each visit will begin with completion of *self-assessment forms*, which will help participants set their own buprenorphine treatment goals, record progress toward goals, and privately report relapse. The behavioral specialist will provide 20-25 minutes of instruction at each visit.

Peer support: Therapeutic groups are a mainstay of addiction treatment because they offer drug users, who are often socially isolated, validation and support from others with similar experiences. The behavioral specialist will facilitate conversation about current opioid use, goals for recovery, and triggers for relapse. We anticipate this will take 20-25 minutes.

Medical Management: Each visit will end with guided relaxation and meditation as a way to calm any heightened emotions from group interactions. The physician will write prescriptions for BMT and address individual concerns (e.g., changes in buprenorphine dosage). Because group medical visits will replace most individual visits, focused histories and physical exams may be necessary and could occur in a private room as needed. If more attention is required for acute symptoms an individual visit can be scheduled at the CHC.

Interaction between primary care physicians (PCPs) and research team: The protocol for communications with referring PCPs will be as follow: 1) G-BMT participants will sign a treatment agreement stating that they will attend group visits weekly and all medication refill requests will go to the group physician; 2) the group physician will send electronic medical record (EMR) messages to the PCP with updates to the treatment plan following each group visit; 3) participants will continue to see their PCP for acute medical care, but not for BMT during the study period; and 4) the group physician will transfer care back to the PCP following completion of the G-BMT intervention through an in-person conversation. The treatment agreement (see appendix), which includes patient and provider expectations, and specifies that all prescriptions will be written at BMT group medical visits, will be discussed at the first group visit and signed by both patients and the G- BMT physician. Subsequently, PCPs will be asked to read and sign the agreement as well. Because this study is developmental, deviations from the agreement (e.g. asking the PCP for a prescription refill following a missed group visit) will be recorded as an outcome for future adaptations to the protocol.

Treatment as usual: Participants randomized to TAU will continue to receive BMT from their PCPs based on a standardized BMT intensification protocol. Prior to the study, PCPs at the CHC will receive one hour of training on BMT intensification. The protocol will require that all BMT patients with persistent opioid abuse receive at least monthly visits with urine drug tests collected at each visit. For participants randomized to TAU, PCPs will receive an automated e-mail reminder about the following protocol. After one urine drug test is positive for opioids, PCPs will increase the frequency of visits to twice monthly with referral for behavioral counseling. After two consecutive positive tests, PCPS will increase visit frequency to weekly. After three consecutive positive tests, PCPs will refer to an addiction specialist or opioid treatment program. We will measure frequency of BMT visits, referral for behavioral counseling and referral to opioid treatment programs during the study. We will determine *observed intensity* of BMT (defined below) for exploratory analyses of treatment outcomes.

Participant tracking: To facilitate tracking participants over the 16 week follow-up period we will use tracking procedures that we developed to retain drug users in our previous research studies, in which we have had an 85% retention rate over 6-month follow-up. On Locator Forms, we will record information about: 1) participants' address and phone number; 2) contact information of participants' family members, friends, case managers, physician, pharmacy, and drug treatment program; and 3) locations where participants hang out.

Data sources and measures: A complete list of measures is listed in Table 1.

Urine Drug Testing: Research visits will include urine drug test collection, which will be used for the primary outcome (both G-BMT and TAU participants will have an equal number of research visits and urines). Urine drug tests collected during G-BMT and TAU medical visits (*clinical drug tests*) will be used for secondary outcomes.

Testing will include opiates, oxycodone, buprenorphine, methadone, cocaine, and benzodiazipines.

Questionnaire: ACASI technology, which plays an audio recording of questions as it displays the question on a computer screen, will be used by the RA to administer questionnaires. After completing the trial, participants and providers will be assessed for satisfaction with treatment. Interviews will take 30-60 minutes depending on the study visit.

Qualitative Interview: We will conduct 20 in-depth semi-structured interviews with persons who have completed the G-BMT intervention in order to better understand the impact of the group buprenorphine maintenance treatment. Interviews will be audio recorded. Interviews will take 45-60 minutes to complete.

Medical records: We will extract electronic medical record data, including visit and prescription information, from Montefiore's health center to assess *medication and visit adherence*, *treatment retention* (see below) and to determine the *observed intensity* of BMT, defined as the number of medical or counseling visits attended during the study period for the TAU arm and the number of group visits attended for the G-BMT arm.

Intervention Materials: The RA will also attend group visits to assess fidelity using a checklist derived from the intervention manual. The RA will document completion of each G-BMT component, time spent on components, and use the checklist to rate facilitators on fidelity to the intervention. The RA will also record participants' attendance, completion of self-assessment forms, and engagement in intervention activities (e.g. # of times gave personal updates). Group cohesion will be measured as part of the ACASI interviews. All group visits will be audio-recorded and at least 25% of recordings will be reviewed by the PI to confirm the assessment of intervention fidelity.

Post-intervention Questionnaires:

Patient Satisfaction: We will adapt a previously published questionnaire that assesses satisfaction with BMT in primary care.[100] Satisfaction is measured in three areas: overall satisfaction, staff expertise/ responsiveness, and helpfulness of treatment. We will adapt the helpfulness domain to address specific components of the G-BMT intervention (e.g. self-assessment forms), and add items that assess privacy and confidentiality.

Provider Satisfaction: We will adapt a previously published questionnaire to assess acceptability of the intervention to participants' PCPs. Satisfaction will be measured in three areas: overall satisfaction with BMT, perceived effectiveness of BMT intensification and support for BMT at the CHC.[101] We will add items for PCPs with patients randomized to the G-BMT intervention to assess satisfaction with communications with the G- BMT team and likelihood of referring patients to group-based BMT in the future.

Table 1. Timing and delivery of intervention and study measures

Measure	Study Instrument	Domain	Assessment Period (week)
Urine			
Opioid use	Observed urine	-	All[†]
Questionnaires			
Sociodemographic information	BHIVES Study[82]	-	0
HIV Risk Behaviors	AIDS risk inventory[93]	-	0, 8, 16
Self-reported drug use	Addiction Severity Index[94]	-	All
Depression	CES-D[95]	-	0, 8, 16
Self-efficacy	DTCQ-8[96]	Self-efficacy	0, 8, 12, 16
Social Support	MSPSS[97]	Outcome Expectation	0, 8, 12, 16
Buprenorphine Knowledge	10 item questionnaire	Knowledge	0, 8, 16
Quality of Life	SF-12[98]	-	0, 8, 16
Group cohesion*	GCQ-S[99]	-	2, 4, 8
Medical Records			
Medical Visits	-	-	1-16
Buprenorphine prescriptions	-	-	1-16
Referrals	-	-	1-16
Opioid use	Clinical urine		1-8
Retention in care	-	-	0, 12, 24
Intervention Materials			
Chronic Health Conditions	-	-	0
Self-assessment forms	Check-list	Goals	1-8
Intervention fidelity	Check-list	-	1-8
Post-intervention Questionnaires			
Patient satisfaction	PCBSS[100]	Barriers and Facilitators	8
Provider satisfaction	5 item questionnaire[101]	-	8
Qualitative Interviews*	Interview Guide		8

*only collected for intervention arm; [†] Study visits (2,4,6,8,12,16 weeks) CES-D = Center for Epidemiologic Studies Depression Scale; DTCQ-8 = Drug-Taking Confidence Questionnaire, 8 item version; MSPSS = Multidimensional Scale of Perceived Social Support; SF-12 = SF-12 Health Survey; GCQ-S = Group Climate Questionnaire – Short Form; PCBSS = Primary Care Buprenorphine Satisfaction Scale

Analysis:

Main outcome variables:

Primary outcome (efficacy): we will use a dichotomous measure (yes/no) of *opioid abstinence* based on 30-day self-reported opioid use following completion of the intervention and the results of urine drug tests (opiates, methadone, oxycodone) at the 8 and 12 week research visits (see Figure 1). Missing urine drug tests will be considered to be positive for opioids.

Secondary outcomes (efficacy):

a.) *Retention in treatment* will be used to determine whether participants remain in BMT following the specified time intervals. *Three month retention* will be defined as having a medical visit or active

buprenorphine prescription 12-16 weeks after study initiation (one month after G-BMT intervention completion). *Six month retention* will be assessed at 24-28 weeks after study initiation.

b.) *Changes in HIV risk behaviors* will be based on the AIDS risk inventory, which includes questions regarding frequency of injection drug use, number of times sharing syringes, number of sexual partners, and frequency of unprotected sex. We will assess risk behaviors at completion of the G-BMT intervention (8 week visit) and two months following completion of the intervention (16 week visit).

Primary outcome (acceptability): Overall satisfaction with BMT will be measured on a 5-point Likert scale for participants and providers.

Primary outcome (feasibility): We will compare *medication and visit adherence* between the G-BMT and TAU arms as the primary measure of feasibility. Medication adherence will be determined from medical record data based on lapses in BMT defined as the number of days without an active buprenorphine prescription during the study. Visit adherence will be defined as the proportion of obligated medical visits (as per G-BMT or TAU protocol) attended. Other important measures of feasibility are listed in Table 2 and will be used as secondary outcomes and to assess fidelity to the G-BMT intervention.

Table 2. Example of feasibility measures for G-BMT

G-BMT component	Measure	Assessment
Overall	Participant engagement # urine drug tests collected Time per group medical visit	RA conducted EMR Timed
Buprenorphine Education	Fidelity to intervention Time for education	Checklist Timed
Self-management skills	Self-assessment forms Fidelity to intervention Time for instruction	Collected Checklist Timed
Peer Support	Personal Updates Feedback to other participants Group Cohesion Time for facilitated discussion	RA observed RA observed GCQ-S* Timed
Medication Management	# non-BMT medical complaints # individual physical exams Time for medical management	EMR RA observed Timed

*assessed as part of ACASI interviews

Analysis: We will use mixed effects logistical regression models incorporating different correlation structures between study arms to account for clustering by group in the intervention arm and by PCP in the TAU arm. For the primary outcomes, abstinence will be the dependent variable and study condition will be the main independent variable. Models will include key covariates that are not equally distributed between study arms.

For each secondary outcome, we will construct a separate mixed effects linear or logistic regression model. In other exploratory analyses, we will determine whether changes in perceived social support or self-efficacy, or the *observed intensity* of BMT mediate the association between study condition and abstinence by using interaction terms for key variables and study condition.

Qualitative Analysis: Analytic Plan. Using NVivo software, analysis of qualitative data will be conducted using a modified grounded theory approach. We will develop a coding scheme that reflects the themes that emerge upon iterative reading of the transcriptions. In grounded theory, themes are not specified prior to analysis, but our modified approach will use the framework of Social Cognitive Theory to organize the themes. With the first 3-5 interviews, preliminary codes will be developed independently by Dr. Fox and the RA. Using the constant comparative method, additional readings of the transcriptions will lead to consolidation of these coding schemes until no further refinement is required. Coding discrepancies will be resolved by consensus. Once coded, these themes will be organized into a conceptual model explaining the impact of group buprenorphine maintenance treatment.

Power Analysis: Based on our experience with the preliminary model of group medical visits, we are confident that we can run five 8-week groups with an average of eight participants during the study period. Therefore, with 40 participants each in the control and interventions arm, the minimally detectable abstinence rate in the intervention arm will be 37%, based on an abstinence rate of 10% in the control arm, an intra-class correlation (ICC) of 0.01, and 80% power. This study may be underpowered to detect a significant difference in our primary outcome (abstinence), but the more important goal of this study is to estimate an effect size for the G-BMT intervention that could be used to design a larger multisite efficacy trial. Based on time and financial constraints, and our also important goals of determining feasibility and acceptability of the G-BMT intervention, we believe that recruiting a larger sample would detract from our ability to study process measures or tailor the intervention further.

Additional adaptations to the G-BMT intervention: We will use data collected in the RCT to further adapt the G-BMT intervention manual. After conducting preliminary analyses of BMT intensity and treatment outcomes, we will have a better understanding of the ideal number of visits for the G-BMT intervention. Patient satisfaction questionnaires will be used to identify specific components of the G-BMT intervention that were not as highly valued as others, and provider satisfaction questionnaires will be used to adapt the protocol for communication between the G-BMT clinicians and PCPs. Checklists evaluating fidelity of the G-BMT intervention will be used to identify components of the intervention that were not completed regularly, which may suggest lack of feasibility. We will review audio recordings of the group visits with the G-BMT clinicians and clarify the reasons for not completing these components. We will assess whether worksheets were completed between visits.

What if participants continue to abuse opioids during the G-BMT intervention? RCTs demonstrate that methadone maintenance is more effective than BMT for severe opioid addiction. In real life settings though, methadone maintenance may be unavailable or unacceptable to opioid users. G-BMT will provide an option for treatment intensification in primary care that currently does not exist. We will ensure safety of research participants by only recruiting patients who already receive BMT from a waivered physician, closely supervising participants during the G-BMT intervention, and facilitating referral to methadone maintenance treatment programs if participants have 3 consecutive urine drug tests that are positive for opioids and they are willing to transfer their care. We will also use an independent data safety monitoring committee to review study outcomes and adverse events every six months of the RCT.

IV. Data and Safety Monitoring Plan

Detailed data and safety monitoring plan. Because this study includes an RCT, we will utilize an internal independent data safety monitoring committee (DSMC).

Protocol Summary: We will conduct a 16-week RCT in primary care to preliminarily test the G-BMT intervention (8 weekly group visits) for efficacy, acceptability, and feasibility in comparison to treatment as usual (TAU) among BMT patients with persistent opioid abuse. Eighty participants with persistent opioid abuse during office-based BMT will receive treatment intensification in the G-BMT intervention or through TAU (i.e. increased frequency of visits with their primary care provider, referral for counseling, and/or referral to addiction specialist). Research visits for data collection will occur at baseline, 2, 4, 6, 8, 12, and 16 weeks after randomization and will include computer-based interviews and urine drug testing. We will also collect electronic medical record data. We will test **efficacy** by collecting interview, urine, and medical record data examining *abstinence* (primary outcome), *retention in treatment*, and *HIV-risk behaviors*, including drug-related and sexually-related risk factors. We will test **acceptability** by assessing patient and provider satisfaction following the trial. We will test **feasibility** by examining process measures, such as *medication and visit adherence* and fidelity to the intervention manual.

Outcome Measures: **Primary outcome (efficacy):** we will use a dichotomous measure (yes/no) of *opioid abstinence* based on 30-day self-reported opioid use following completion of the intervention and the results of urine drug tests (opiates, methadone, oxycodone) at the 8 and 12 week research visits. Missing urine drug tests will be considered to be positive for opioids.

Secondary outcomes (efficacy): 1.) *Retention in treatment* will be used to determine whether participants remain in BMT following the specified time intervals. *Three month retention* will be defined as having a medical visit or active buprenorphine prescription 12-16 weeks after study initiation (one month after G-BMT intervention completion). *Six month retention* will be assessed at 24-28 weeks after study initiation.

2.) *Changes in HIV risk behaviors* will be based on the AIDS risk inventory, which includes questions regarding frequency of injection drug use, number of times sharing syringes, number of sexual partners, and frequency of unprotected sex. We will assess risk behaviors at completion of the G-BMT intervention (8 week visit) and two months following completion of the intervention (16 week visit).

Primary outcome (acceptability*)*: Overall satisfaction with BMT will be measured on a 5-point Likert scale for participants and providers.

Primary outcome (feasibility): We will compare *medication and visit adherence* between the G-BMT and TAU arms as the primary measure of feasibility. Medication adherence will be determined from medical record data based on lapses in BMT defined as the number of days without an active buprenorphine prescription during the study. Visit adherence will be defined as the proportion of obligated medical visits (as per G-BMT or TAU protocol) attended. Other important secondary outcomes will be measures of feasibility from assessments of fidelity to the G-BMT intervention based on audio-recordings and observations of the group medical visits.

Inclusion/exclusion criteria*:* 1) Currently receiving BMT at the CHC; 2) Received BMT for ≥ 12 weeks; 3) Persistent opioid abuse (urine drug testing positive for an unprescribed opioid in the previous 6 months); 4) ≥18 years old; 5) fluent in English or Spanish. Pregnant women and patients who show contraindications to BMT (alcohol use disorder; benzodiazepine use disorder; unstable mental health condition) will be excluded.

TRIAL MANAGEMENT

Enrolling Clinics*:* Participants will be recruited from the Comprehensive Health Care Center (CHCC) of Montefiore Medical Center. CHCC offers primary and specialty care to over 15,000 adult patients and is representative of those serving low-income urban neighborhoods. Over 65% of patients have public insurance and most live in the surrounding neighborhoods of the South Bronx, which are 57% Hispanic and 39% Non-Hispanic Black, and remain devastated by drug use and HIV/AIDS. The buprenorphine treatment program at CHCC has provided BMT to more than 700 patients since 2006, and has been used extensively for BMT-related clinical research. The CHC has assisted in recruitment and retention of study subjects, and electronic medical records can easily be extracted to ascertain study outcomes.

Projected time table: Study activities will be conducted in accordance with the timeline below. Our target enrollment is 80 participants over a 12 month period in years 2 and 3.

Timeline	Year 1				Year 2				Year 3			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Hire and train staff	X											
Submit IRB application	X											
Aim 1: Focus groups and open-ended interviews		X										
Aim 1: Analyze qualitative data			X	X								
Aim 2: Develop manual for G-BMT intervention				X	X							
Aim 2: Testing materials and refinement					X							

Target populations distribution*:* Based on prior research conducted at CHCC's buprenorphine treatment program, we expect that the population will be 70% Male/30% Female, 60% Hispanic/35% Non-Hispanic Black/5% Non-Hispanic White, and mostly middle age (40-50 years old). Therefore we expect to enroll 56 men and 24 women; 48 Hispanic, 28 Non-Hispanic Black and 4 Non-Hispanic White participants. The buprenorphine treatment program at CHCC does not treat adolescents less than 18 years old.

DATA MANAGEMENT AND ANALYSIS

Data acquisition and transmission*:* We will collect interview data, urine samples for drug testing, intervention materials and audio recordings from group medical visits, and we will extract electronic medical records.

Interview data will be collected via audio computer-assisted self-interview (ACASI) technology at baseline and during research visits 2, 4, 6, 8, 12, and 16 weeks following enrollment. *Urine samples* will be collected for drug testing at baseline and during research visits 2, 4, 6, 8, 12, and 16 weeks following enrollment. Urine drug tests will be conducted at the community health center using commercially available rapid urine drug test. At these research visits, the RA will ask subjects to provide a urine specimen in a private bathroom while the RA stands outside the door listening for tampering. Results of urine drug tests will be recorded on a standardized paper form only using the participants study ID and not other personal identifiers. *Feasibility* measures will be collected by the research assistant (RA) who will observe, time, and collect written intervention materials (e.g. self-assessment forms) from group visits. We plan to run 5 cycles of group visits, therefore, these field notes will be marked with the cycle number and group visit number but will not contain participant identifiers. *Written intervention materials* will be marked only with a study ID and transported directly to the research offices following weekly meetings between Dr. Fox (PI) and the research team. Materials will be stored in locked file cabinets. *Audio recordings* of each group visit and qualitative interviews will be collected by the RA using a digital audio-recording device. After each group visit or qualitative interview, audio recordings will be transferred to a single password protected encrypted computer and then erased from the recording device. Audio recordings will be uploaded to a secure internet portal for professional transcription and then will be transcribed with blinding of any references to personal identifiers.

Medical record data will be electronically extracting from Montefiore's centralized clinical database, and will include buprenorphine prescription data, and data on clinical visits (medical and counseling) and chronic health conditions. The electronic file will be created by Montefiore health technology staff, emailed to the PI in a password protected file, and saved on an encrypted password protected computer.

Data entry method*:* At enrollment, the RA will administer interviews using ACASI technology. Interview data will be directly entered on a lap top computer, which will be password protected, and will contain only participant study ID (no other identifying information). Additional data (e.g. urine drug test results) will be entered into a password-protected Redcap database by two separate, trained data entry staff, and discrepancies will be corrected by Dr. Fox based on source documents.

Data analysis plan*:* We will use mixed effects logistical regression models incorporating different correlation structures between study arms to account for clustering by group in the intervention arm. For the primary outcomes, abstinence will be the dependent variable and study condition will be the main independent variable. Covariates will include depressive symptoms and sociodemographic variables that are associated with the study condition in bivariate testing. For each secondary outcome, we will construct a separate mixed effects linear or logistic regression model with similar adjustments. In other exploratory analyses, we will determine whether changes in perceived social support or self-efficacy, depressive symptoms, or intensity of the intervention (i.e. # of group sessions attended) mediate the association between study condition and abstinence by using interaction terms with these variables and study condition. We will also determine whether sub-groups of patients (e.g. those with low perceived social support) benefit most from group participation.

QUALITY ASSURANCE

Validity and integrity: For interview data, participants will enter data directly into a laptop computer, but the RA will be available to answer any questions about interview. We will develop the computerized ACASI interviews so that there are limits on the potential responses that can be entered. The research assistant will also record and intervene if participants appear to be responding to questions too rapidly or in a mechanical way, which may indicate a problem with data integrity. Urine drug tests will be conducted at the community health center using commercially available rapid urine toxicology tests. To ensure validity and integrity of the urine samples, all urine samples will be collected by research staff. The RA will ensure that participants will not enter the private bathroom with jackets, purses, or any personal affects. The RA will stand outside of the bathroom to listen for possible tampering. In addition, research staff will ensure that the urine is warm (cold urine could indicate adulteration). Feasibility measures and written intervention materials will be collected using standardized paper forms by a trained research assistant. Protocol manuals and training of research assistants will include detailed discussion of the importance of recording reliable, valid data when observing group visits. Dr. Fox will review 25% of audio recordings from group visits to confirm fidelity to the intervention manual.

Accuracy and completeness: To ensure completeness of attendance at group visits, participants will receive a round-trip transit pass (worth $5.50), which will facilitate transportation to and from the community health center. To ensure completeness of data collection, we will provide compensation ($25) for each of the six research visits when interview and urine samples will be collected.

To ensure accuracy and completeness of interview data, we will program the ACASI interview such that participants will be required to answer each question before they can move on to the next question. If participants would like to skip a question, they will be able to inform the RA who will then advance the computer to the next question. Accuracy will be facilitated by using a touch screen computer (rather than a keyboard or mouse) which is likely to reduce participant errors. Data entry will not be required for interview data because participants directly enter their answers into the computer.

To ensure completeness of electronic medical record data, we will work closely with the electronic medical record extractor to ensure this process achieves accurate prescription and visit information for all participants. We have used similar procedures in prior studies. Dr. Fox will review the entire medical record of the first 10 participants to ensure that medical records match the extracted data. If there are inconsistencies between the medical records and extracted data, we will work with the extractor to revise procedures.

Data quality will be monitored by random inspection of the completed ACASI files and research documents by Dr. Fox every three months. Any problems detected will be addressed and discussed in collaboration with Co-Investigators. If necessary, retraining of the RA observing group visits will be conducted.

Collected intervention materials will be securely transported to the Principal Investigator's data entry site, and data will be entered by the data entry staff into a password protected computerized database. Prior to conducting analyses, data cleaning will be performed to eliminate duplicate and invalid data.

REGULATORY ISSUES

Reporting of SAEs*:* Serious adverse events will be reported to the DSMC, Einstein IRB, and NIDA within 48 hours via phone, written report or fax. We will utilize Einstein's Reportable Events Form for all reports to the IRB. We will log all SAEs and report to the DSMC, Einstein IRB, and NIDA, in summary form annually. As per Einstein IRB policy, unanticipated (non-serious) adverse events do require reporting to the IRB, but these will be documented in the AE log.

Reporting of IRB actions to NIDA*:* Dr. Fox will report all relevant IRB actions, including protocol deviations, adverse events, and serious adverse events in summary form to the Program Officer at NIDA on an annual basis as part of the progress report.

Report of changes or amendments to the protocol: All changes to the protocol will be submitted to the

Einstein IRB for review and approval prior to implementation. Any protocol deviations will be reported to the Einstein IRB within 10 days on a standard IRB protocol deviation reporting form, and corrective action will be implemented as necessary. Reports to the data safety monitoring committee will occur every six months and will include information about any amendments to the protocol and any protocol deviations. Amendments to the protocol will be reported to the Program Officer at NIDA in annual progress reports.

Trial stopping rules*:* Interim analysis of the data will be conducted when 50% of the sample has accrued (N = 40). If the results show overwhelming, statistically significant differences in opioid abstinence or retention in treatment between the intervention and TAU arms, the study will be stopped. If we find that buprenorphine treatment discontinuation or serious adverse events are significantly more likely in the TAU arm compared to the G-BMT arm (e.g., if primary care providers stop buprenorphine treatment because of persistent opioid abuse), the randomized study will be halted. If the study is halted due to the results of an interim analysis, the study may still continue as a one-arm trial (e.g., all subjects will participate in the G-BMT intervention until 80 participants have enrolled) in order to collect additional process measures on conducting group visits.

Interim analyses will be conducted by Dr. Fox with close feedback from the biostatistician. The research team, in collaboration with the DSMC and the Program Officer of NIDA will review all pertinent data to determine whether to continue accrual. A decision to stop the study may be made at any time that the research team and DSMC agrees that an unacceptable type and/or frequency of adverse events has been observed. Dr. Fox will report the decision to terminate the study to the DSMC, IRB and NIDA within 48 hours of this determination. He will submit a narrative description of the reasons for early termination of the study to the IRB and NIDA within 10 days.

Disclosure of conflict of interest: Prior to IRB approval and protocol initiation, all key personnel are required to disclose any financial interest that they, their partners, or their dependent children have related to the research or its sponsor. Potential financial interests include anything of monetary value, including cash, stocks or other ownership interests, and patents, copyrights, or other property rights. Key personnel are instructed to notify the Einstein IRB promptly if a change in conflict of interest occurs during the course of the study and are queried on changes every 90 days. Potential conflicts of interest are also reassessed annually during annual progress reports to the Einstein IRB.

TRIAL SAFETY

Potential risks for participants*:* The primary risks of this study are: (1) Breach of confidentiality leading to embarrassment or dismissal from buprenorphine treatment program; (2) inconvenience and discomfort associated with interviews or urine drug testing; (3) fear that refusal to participate will affect care at the healthcenter; (4) stress imposed participants due to group interactions; (5) continuing BMT despite ongoing opioid abuse; (6) burden of

attending an increased number of medical visits following intensification of BMT

Confidentiality issues: We will collect personal information from participants to facilitate tracking, and we will be asking personal questions including substance use and HIV risk behaviors. We have outlined our procedures to maintain confidentiality below.

Inconvenience and discomfort associated with interviews or urine drug testing: Participants will be asked about substance use, psychosocial distress, and opioid addiction treatment. Urine drug testing will be conducted by research staff. It is possible that such questions and procedures could produce anxiety in participants.

Fear that refusal to participate will affect care or services: Participants must have a doctor at Montefiore's community health center as part of inclusion criteria. In the informed consent process, they will be clearly instructed that refusal to participate will in no way affect their care at the affiliated health center.

Stress imposed on participants due to group participation: There will be a board certified physician and behavioral specialist at each group medical visit. Drs. Fox and Gonzalez will also be available to intervene if participants express high levels of distress during group medical visits. Drs. Fox and Gonzalez will review audio recordings of group sessions and have regular meetings with study clinicians to inquire about distress or conflict during group sessions.

Continuing BMT despite ongoing opioid abuse: We are selecting for a population with persistent opioid abuse, and these individuals may need a higher level of treatment intensity than can be offered in primary care settings.

Burden of attending an increased number of medical visits following intensification of BMT: Participants randomized to the G-BMT intervention will be expected to attend weekly group visits during the 8 week intervention. Participants randomized to the TAU arm will also likely be required to attend an increased number of medical visits, because PCPs will follow an intensification of BMT protocol that instructs them to increase visits to twice monthly or weekly if participants continue to abuse opioids. The increased number of visits could be burdensome and negatively affect adherence to buprenorphine treatment if participants missed medical visits and had lapses in their buprenorphine prescriptions.

Recruitment and informed consent: We will obtain informed consent for all participants of the RCT prior to collecting any information with personal identifiers (e.g. locator form or medical record release forms), administering the baseline ACASI interview, and randomization to an intervention arm. Informed consent will be obtained by the RA.

Protection against risk: We will institute the following processes to ensure confidentiality is maintained: We will create a system that prevents linking sensitive material to participants' personal identifiers. We will have a "name-based" system and "ID-based" system that will remain all documents that have patient identifiers will be filed together. Some of these documents will have participants' signatures (e.g. consent forms) and others will have personal information (e.g. locator forms).

In the ID-based system, all documents that do not include identifying information or signatures will use participants' IDs (rather than names), and will be filed together. All forms will contain either participants' names or their study IDs, but not both. We will maintain one electronic document that links participants' names and study IDs, which will be stored on a password-protected computer.

1. We will obtain a Certificate of Confidentiality to protect participants' sensitive information.
2. Letters and/or phone messages that are left for participants (reminders of group medical visits or to schedule research visits) will not include any personal identifying information, and will not mention buprenorphine treatment.
3. Study records will be kept in locked files and/or within limited access, password-protected computer files, available only to the investigators and study personnel.
4. Publication or presentation of study results will not identify subjects by name.

Management of inconvenience, discomfort, and distress: In addition to addressing issues of confidentiality, it is crucial that we protect participants from psychological distress that may occur during any of the intervention or research activities. Participants will be instructed that they may withdraw from the study if this occurs. Dr. Fox will be contacted by cell phone if any study participants become overly distressed. Dr. Fox (a board-certified general internist) will be involved with all study activities and will assess for severe discomfort or other severe problems. Dr. Gonzalez (a clinical psychologist) will also be available to assess participants with high levels of distress. Depending on severity of the problem, participants may be escorted to either Montefiore's community health center or emergency department. Participants may be referred for individual medical or psychiatric attention at Montefiore's community health center or the emergency department (depending on severity).

Continuing BMT despite ongoing opioid abuse: Participants with three consecutive urine drug tests that are positive for opioids during group medical visits will be offered facilitated referral to methadone maintenance treatment program; however, some may refuse referral. In the G-BMT intervention arm, the research team will meet to discuss the risks and benefits of continuing BMT and participation in group medical visits. In the TAU arm, continuation of BMT will be up to the prescribing physician. If there is concern that risks of continuing treatment outweigh the potential benefits, the participant will be removed from the trial and referred to an

addiction specialist.

Burden of BMT intensification: We will collect data on adherence to medication and visits as a feasibility measure, and we will monitor treatment, after 50% of the sample has accrued.

Potential benefits for participants: Group visits have the potential to improve rates of opioid abstinence thereby reducing HIV risk behaviors and overdose risk. Our preliminary work on buprenorphine group visits has demonstrated that they are highly valued, therefore, other benefits, such as reductions in depressive symptoms or distress, may lead to improved health status.

Collection of AEs and SAEs*:* Because the research visits will include computerized interviews and urine collection, and the G-BMT intervention will include group counseling and buprenorphine education, participants are likely to incur no more than minimal risk of AEs. However, if AEs occur, they are likely to include psychological distress. AEs will be collected by members of the research team as they conduct research visits or group visits, and will be reported to Dr. Fox either immediately (for serious AEs) or during regular weekly project meetings (for non-serious AEs). Serious AEs could include death, life-threatening adverse reaction, inpatient hospitalization, persistent disability, or an event jeopardizing the participant's health.

Reporting of AEs and SAEs: Consistent with the policies of the Einstein IRB, all adverse events (AEs) will be reported to Dr. Fox, who will maintain a log of AEs and will decide about the need to report to the IRB. All serious adverse events (SAEs) will be logged and reported to the DSMC, Einstein IRB, and NIDA within 48 hours. We will utilize the Einstein Reportable Events Form for reports to the IRB. Unanticipated (non-serious) adverse events do not require reporting to the IRB. All deaths will be reported to the DSMC, IRB, and NIDA within 48 hours.

Management of SAEs or other study risks*:* Dr. Fox will be contacted by cell phone if any study participants become psychologically distressed. Dr. Fox (a board-certified general internist) will make a clinical assessment or the participants' health and safety. Dr. Gonzalez (a clinical psychologist) will also be available to assess participants with high levels of distress. Depending on severity of the problem, participants may be escorted to either Montefiore's community health center or emergency department. Participants may be referred for individual medical or psychiatric attention at Montefiore's community health center or the emergency department (depending on severity). We have also set up several precautions to prevent breach of confidentiality and these have been described above.

TRIAL EFFICACY

Interim analysis of efficacy data: Interim analysis of the data will be conducted when 50% of the sample has accrued. If the results show overwhelming, statistically significant differences in opioid abstinence or retention

in treatment between the intervention and TAU arms, the study will be stopped. If we find that buprenorphine treatment discontinuation or serious adverse events are significantly more likely in the TAU arm compared to the G-BMT arm (e.g., if primary care providers stop buprenorphine treatment because of ongoing opioid abuse), the randomized analysis, the study may still continue as a one-arm trial (e.g., all subjects will participate in the G-BMT intervention until 80 participants have enrolled) in order to collect additional process measures on conducting group visits.

DSM PLAN ADMINISTRATION

Responsibility for data and safety monitoring*:* The Principal Investigator, Dr. Fox, will be responsible for monitoring the safety and efficacy of this trial, executing the data and safety monitoring plan, and complying with the reporting requirements. The DSMC will vote on approval of the protocol prior to initiation of the RCT and submit meeting minutes to the IRB within 30 days. The DSMC will review safety and trial progress and provide advice with respect to study continuation, modification, and/or termination.

Frequency of DSM reviews: We will conduct continuous, close monitoring by study staff and investigators, with prompt identification and reporting of adverse events. Information about all unanticipated and serious adverse events will be reported as described above. The Principal Investigator will provide a summary of the data and safety monitoring report to the Program Officer at NIDA on an annual basis as part of the progress report. The DSMC will meet every 6 months and as needed in-person or via conference call.

Content of DSM report: Dr. Fox will provide a summary of study activities to the DSMC every 6 months. This will include the number of participants screened, enrolled, and lost to follow up; all adverse events; all pregnancies; and all protocol deviations.

The Principal Investigator will provide a summary of the data and safety monitoring report to the Program Officer at NIDA on an annual basis as part of the progress report. The data and safety monitoring report will include a brief description of the RCT, and a summary of baseline sociodemographic characteristics of participants enrolled to that point. The report will include a summary of the total number of participants screened, enrolled, and lost to follow up; and quality assurance or regulatory issues that have taken place in the past year; all actions or changes taken by the IRB with respect to the protocol; and all unanticipated adverse events (AEs) and Serious Adverse Events (SAEs). If applicable, the data safety and management report to NIDA will also include the results of any efficacy data analyses conducted.

DSM BOARD PLAN

Members and affiliation: We will establish a data and safety monitoring committee (DSMC) for the proposed study. This committee will include faculty members at the Albert Einstein College of Medicine who

are unaffiliated with the study. We have chosen committee members based on their scientific and clinical experience and expertise in opioid addiction treatment and design of randomized controlled trials. Members of the DSMC will be: 1) Shadi Nahvi, MD MS, Assistant Professor of Medicine who is an expert in addiction treatment and methadone maintenance treatment provider; 2) Ellen Silver, PhD, Associate professor of Pediatrics, who is an expert in behavioral interventions to reduce HIV risk; and 3) Ellie Schoenbaum, MD, Professor of Medicine, Epidemiology & Population Health, and Obstetrics & Gynecology and Women's Health, who has extensive experience studying HIV and drug use and in conducting randomized controlled trials.

Frequency of meetings: Every 6 months, reports will be emailed to DSMC members summarizing the number of participants screened, enrolled, and lost to follow up; all adverse events; all pregnancies; and all protocol deviations. The DSMC will meet every 6 months and as needed in-person or via conference call.

Conflict of interest: The DSMC will be comprised of individuals who are unaffiliated with the study, and who have no financial interests related to the research or its sponsor.

Protection of confidentiality: Measures to ensure the confidentiality of research participants is outlined above. Monthly DSMC reports will not identifying participants by name. Should IRB or DSMC members request to review study records, we will request that all protected health information be treated confidentially.

Monitoring activities (initial and ongoing study review): The DSMC will meet and vote on approval of the protocol prior to initiation and the minutes of the meeting will be submitted to the IRB within 30 days. It will review safety and trial progress and provide advice with respect to study continuation, modification, and/or termination.

Communication plan to IRB, NIDA and FDA: In accordance with Einstein IRB regulations, the DSMC will record minutes of all meetings. The minutes will include the following: 1) attendance, 2) summary of the discussion, and 3) findings, (e.g., research may begin or continue, recruitment is halted, actions needed to re-open recruitment, etc.). The DSMC will send the investigator and the IRB all minutes. If the DSMC concludes that the protocol should continue, unmodified, the DSMC will send the investigator and the IRB the minutes, and no further action will be taken. If the DSMC concludes that changes to the protocol and/or the informed consent are required, but recruitment may continue, the PI will submit an amendment to implement the required changes for review by the IRB. If the DSMC concludes that recruitment should be stopped: 1) the DSMC will send the investigator the minutes with directive to suspend recruitment immediately; 2) the DSMC and the Einstein IRB will copy each other on all written and electronic communications; 3) the IRB Chair or designee will review the DSMC recommendations, and if in agreement, 4) the IRB will notify the investigator, in writing, affirming the DSMC action, and directing the investigator to submit an amendment to

implement the required changes; and 5) the PI will submit an amendment to implement the required changes for review by the IRB.

Any serious adverse event, whether or not it is related to study interventions, will be reported to the DSMC, the IRB, and the Program Officer at NIDA within 48 hours by phone, email or fax. The initial SAE report will be followed by submission of a completed SAE report to all of these institutions within 5 days. All adverse events will be compiled, and reported in summary form to the DSMC and the Einstein IRB annually and at the conclusion of the study. A summary of the SAEs that occurred during the previous year will be included in the annual progress report to the IRB and to NIDA. Dr. Fox will report all DSMC recommendations and IRB actions, including protocol amendments in summary form to NIDA on an annual basis as part of the progress report.