Adaptation of the Friendship Bench Counseling Intervention to Improve Mental Health and HIV Care Engagement Outcomes among People Living with HIV Who Inject Drugs in Vietnam

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Adaptation of the Friendship Bench counseling intervention to improve mental health and HIV care engagement outcomes among people living with HIV who inject drugs in Vietnam

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Protocol Chair: Bradley N. Gaynes

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ABSTRACT

Injection drug use is the primary driver of the HIV epidemic in Southeast Asia. In 2017, the HIV prevalence among people who inject drugs (PWID) in Southeast Asia was 15%. PWID, most of whom have opiate use disorder (OUD), have low rates of HIV testing, retention in care, antiretroviral therapy (ART) initiation, and viral suppression. PWID also experience high rates of HIV-related and all-cause mortality. Common mental disorders (CMDs), including depressive, anxiety, and stress-related illnesses, occur in 40-50% of PLWH and OUD and are strongly associated with negative outcomes for HIV patients, including worsening course of HIV, more rapid progression to AIDS, increased ART non-adherence, and increased mortality rates.

To respond to the great need for mental health treatment in low- and middle-income countries, the global mental health field has focused on developing task-shifting and integration approaches that equip non-specialists to deliver evidence-based mental health interventions at scale. However, such task shifting interventions to address CMDs have received limited attention in Southeast Asia among OUD. Vietnam, with its high prevalence of PLWH and OUD, its integration of methadone maintenance therapy with HIV care, and its priority for developing CMD care for this population, is an ideal setting to evaluate task-shifting mental health approaches to address CMDs and improve HIV care outcomes.

The Friendship Bench (FB) is a feasible and effective task-shifting mental health intervention designed for low-resource settings that is a strong candidate to address CMDs in this population. FB is a problem solving therapy-based intervention with demonstrated effectiveness treating CMDs among primary care patients when delivered by lay counselors. Lay counselors may effectively deliver FB to PLWH with OUD, but CMD may prove more difficult to treat in patients with OUD and require professionally trained counselors to be effective.

Our objective in this proposal is to complete a pilot randomized trial of 75 patients from 4 MMT clinics in Hanoi. Our specific aims are: 1) To adapt the Friendship Bench (FB) protocol to be optimized for PLWH and OUD in Vietnam; and 2) To evaluate the feasibility, fidelity, and acceptability of the adapted FB as well as preliminary indicators of its impact in improving CMDs and HIV care and drug use treatment outcomes. The Friendship Bench approach has the potential to make an important contribution to address CMDs and reduce barriers to HIV treatment success among PLWH with OUD, a critical population driving the HIV epidemic in Vietnam and many Southeast Asian countries. This proposal will generate critical evidence for designing a fully powered clinical trial to test our adapted FB protocol in improving HIV, mental health, and drug use treatment outcomes for this vulnerable population.

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HISTORY OF PROTOCOL CHANGES

Version 1.0, 21 May 2020

- None to date.

Version 2.0, 23 September 2020

- Addition of formative phase in-depth interviews and focus groups to Section 3, Aim 1.

Version 3.0, 1 October 2023

- Updated outcome measures.

PROTOCOL TEAM ROSTER

UNC Principal Investigator

Bradley Gaynes, MD, MPH
UNC School of Medicine
Department of Psychiatry
CH# 7160, 130 Mason Farm Rd
Chapel Hill, NC 27599 USA
Phone: 919-445-0214
Fax: 919-445-0234
Email: bradley_gaynes@med.unc.edu

Co-Investigators

Brian Pence, PhD, MPH
UNC School of Public Health
Department of Epidemiology
CB# 7435, 2102-E McGavran-Greenberg
Chapel Hill, NC 27599-7435, USA
Phone: 1-919-966-7446
Fax: 1-919-966-2089
Email: bpence@unc.edu

Vivian Go, PhD
UNC School of Public Health
Department of Health Behavior
CB# 7440, 361 Rosenau Hall
Chapel Hill, NC 27599-7440, USA
Phone: 1-919-966-3908
Fax: 1-919-966-2921
Email: vgo@email.unc.edu

Dr. Le Minh Giang
Hanoi Medical University
1 Ton That Tung Street
Room 605, Building A1
Hanoi, Vietnam
Phone: 84435746825
Fax: n/a
Email: leminhgiang@hmu.edu.vn

Dr. Viet Tran Ha
UNC School of Public Health
Department of Health Behavior
Yen Hoa Health Clinic, Lot E2, Duong Dinh Nghe Street
Yen Hoa Ward, Cau Giay District
Hanoi, Vietnam
Phone: 84912785886
Fax: n/a
Email: vietha@live.unc.edu

Dr. Dixon Chibanda
The Friendship Bench Trust
4 Weale Road, Milton Park
Harare, Zimbabwe
Phone: n/a
Fax: n/a
Email: dichi@zol.co.zw;
dixon.chibanda@friendshipbench.io

Dr. Ruth Verhey
The Friendship Bench Trust
4 Weale Road, Milton Park
Harare, Zimbabwe
Phone: n/a
Fax: n/a
Email: ruth.verhey@friendshipbench.io

GLOSSARY OF TERMS/ACRONYMS

AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral Therapy
CDC	Center for Disease Control
CMD	Common Mental Disorder
DASS-21	Depression, Anxiety, and Stress Scale -21
EUC	Enhanced Usual Care
FB	Friendship Bench
GEE	generalized estimating equation
HIV	Human Immunodeficiency Virus
IRB	Institutional Review Board
LMIC	Low- and Middle-Income Country
MINI	Mini International Neuropsychiatric Interview
MMT	Methadone Maintenance Therapy
MOH	Ministry of Health
NIDA	National Institute of Drug Abuse
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
OUD	Opiate Use Disorder
PI	Principal Investigator
PLWH	People Living with HIV
PST	Problem-solving Therapy
PWID	People Who Inject Drugs
RCT	Randomized Clinical Trial
SAE	Serious Adverse Event
UNC	University of North Carolina

1.0 INTRODUCTION

This project will adapt and pilot a feasible and effective problem-solving therapy designed for low-resource settings to address common mental disorders like depression and anxiety – the Friendship Bench– in a Vietnamese population of individuals living with HIV who also have opiate use disorder. The Friendship Bench approach has the potential to make an important contribution to address CMDs and reduce barriers to HIV treatment success among PLWH with OUD, a critical population driving the HIV epidemic in Vietnam and many Southeast Asian countries. This proposal will generate critical evidence for designing a fully powered clinical trial to test our adapted FB protocol in improving HIV, mental health, and drug use treatment outcomes for this vulnerable population.

1.1 Background and Literature Review

Injection drug use is the primary driver of the HIV epidemic in Southeast Asia.[1] Parenteral exposure to infected blood is one of the most efficient means of HIV transmission,[2-4] which has resulted in rapid and uncontrolled HIV epidemics among PWID.[5] In Southeast Asia, as in many other LMICs, HIV prevalence among people who inject drugs (PWID) is several times higher than HIV prevalence in the general population and involves users from all genders.[5] In 2017, the HIV prevalence among PWID in Southeast and Central Asia was 15% and 11%, respectively.[6] PWID, most of whom have OUD, who are living with HIV have low rates of retention in care, antiretroviral therapy (ART) initiation, and viral suppression,[7-10] reflecting the marginalized and stigmatized nature of this group.[11] PWID also experience high rates of HIV-related and all-cause mortality at all stages of the HIV care continuum.[12-14] Policy makers have identified the urgent need to increase the reach and effectiveness of HIV treatment programs in this population.[5,11,15]

Common mental disorder (CMDs), a collective term referring to depressive, anxiety, and stress-related disorders,[16] are highly prevalent among PLWH and OUD.[17-21] Depression is the most common psychiatric comorbidity – and one of the most common comorbidities overall – among adults living with HIV worldwide.[22,23] Depression affects an estimated 20-40% of people living with HIV.[22,24-29] Anxiety or traumatic stress disorders are also common, occurring in 10-20% of HIV-infected individuals,[30] and are often comorbid with MDD in this population.[18,27,28,31,32] Compared to the general population of people living with HIV, PWID living with HIV are even more prone to CMDs due to economic hardship, incarceration, and HIV and drug related stigmatization and discrimination.[33,34] One study reported that the prevalence of moderate to severe depressive and anxious symptoms among PWID living with HIV was 69%[35] with up to 63% meeting diagnostic criteria for a depressive disorder.[19-21]

Despite serious consequences of mental illness on health and HIV progression, mental illness remains under-diagnosed and under-treated in HIV populations, especially in LMIC countries, such as many countries in Southeast Asia.[36] In LMICs, between 76% and 85% of people with mental disorders receive no treatment for their disorder,[37] with an even greater risk for under treatment for those with HIV and coexisting substance use.[36] Collectively, the cluster of diagnoses – HIV, common mental disorders, and substance abuse disorders – has emerged as a distinct clinical condition wherein patients experience a complex set of medical, psychological and social complications that need to be tackled through integrated care.[38] Treatment for mental health conditions is a critical step in improving the emotional and physical well-being of HIV-infected PWID.[39,40] While appropriate management tools are increasingly available,[18,41-45] healthcare services for CMDs remain scarce in LMICs.[46,47]

Feasible and effective task-shifting mental health interventions are key to addressing this need. To respond to the high burden of mental disorders globally and the vast unmet need for mental health treatment in low and middle income countries,[48] the global mental health field has focused on developing task-shifting and integration approaches that equip non-specialists to deliver evidence-based mental health interventions at scale.[49] Such approaches will be critical to respond to the large unmet need for mental health treatment among PLWH/OUD. However, such task-shifting interventions to address CMDs among PLWH and OUD have received limited testing in Southeast Asia.

1.2 Study Rationale

Vietnam is an ideal setting to evaluate the potential of task-shifting mental health approaches to address CMDs and improve HIV care outcomes among PLWH and OUD. First, as with other countries in Southeast Asia, the HIV epidemic in Vietnam is heavily concentrated among those with OUD (primarily heroin). Vietnam has been identified as one of six countries accounting for half of the global population of PWID, with the prevalence of HIV among this group ranging from 15-30%.[15,50,51] Second, the Vietnam Ministry of Health (MOH) has dramatically expanded methadone maintenance therapy (MMT) clinics for those with OUD as well as integrated MMT/ART care for PLWH with OUD; this integrated care model, providing HIV treatment in the MMT clinics where most individuals with OUD receive care, provides an ideal platform to additionally address CMDs. Third, the Vietnam MOH has prioritized development of CMD care for PLWH and OUD.[52] Nevertheless, substantial barriers to care exist. Key challenges to mental health treatment in the general population in Vietnam include the lack of mental health legislation and of personnel and psychiatric facilities, and few mental health treatment resources are currently available to this highly stigmatized population.[53,54]

The Friendship Bench (FB) is a feasible and effective task-shifting mental health intervention designed for low-resource settings that is a strong candidate to address CMDs in this population. FB is a problem solving therapy-based intervention with demonstrated effectiveness in addressing CMDs among primary care patients when delivered by lay counselors.[55] FB is designed to respond to CMDs generally rather than one psychiatric diagnosis specifically, and to meet the needs of low-resource settings with few mental health specialists.

Lay counselors may prove effective in delivering FB to PLWH with OUD; indeed, in other work we have demonstrated the effectiveness of peer counselors in improving ART adherence in this population.[56] That said, CMDs may prove more difficult to treat in a population with OUD than among primary care patients,[39,57] requiring the higher skill level of professional counselors for FB to be effective with this key population. A number of health care professionals in Vietnam have training in counseling, and the MOH could invest in expanding this cadre if evidence suggests that the higher level of training is critical. However, if lay counselors are equally effective then their deployment would be less expensive.

Our ***objective*** is to complete a pilot randomized trial of 75 patients from 4 MMT clinics where we have worked successfully in the past. We will compare FB delivered by professional counselors and FB delivered by lay counselors vs. enhanced usual care to improve CMDs and HIV care outcomes among PLWH and OUD in Vietnam. This work will

generate critical data to inform a fully powered R01 trial. We ***hypothesize*** that adapted FB will be acceptable to patients and providers, prove feasible to integrate into MMT clinics, be delivered with fidelity, and demonstrate preliminary indications of impact with both counselor groups.

2.0 HYPOTHESES AND STUDY OBJECTIVES

2.1 Hypotheses

There are not specific hypotheses for this pilot study. Our ***objective*** in this proposal is to complete a pilot randomized trial of 75 patients from 4 MMT clinics in Hanoi.

We will adapt the evidence-based FB intervention for the specific needs of adult PLWH and OUD in Vietnam (Aim 1).

We will then pilot the adapted FB protocol in a three-armed randomized controlled pilot trial (*professional counselors, lay counselors, or enhanced usual care*) with 75 adult HIV patients with OUD. We will assess feasibility and acceptability of the adapted FB protocol through semi-structured interviews with patients and providers, while evaluating fidelity of delivery and preliminary indicators of impact in improving HIV (primary outcome in subsequent R01), mental health (secondary), and drug use treatment (secondary) outcomes (Aim 2)

2.2 Study Objectives

AIM 1: To adapt the proven Friendship Bench (FB) protocol to be optimized for PLWH and OUD in Vietnam.

Key outcome of Aim 1. The primary outcome of Aim 1 will be the finalized revised FB protocol that is adapted for PLWH and OUD in Vietnam.

AIM 2: To assess the feasibility, fidelity, and acceptability of the adapted FB as well as preliminary indicators of its impact in improving CMD and engagement in HIV care and drug use treatment via a small three-arm individually randomized trial, comparing FB by professional counselors to FB by lay counselors to enhanced usual care for PLWH and OUD with CMDs.

The ***primary outcomes*** of the pilot trial will be the feasibility, acceptability, and fidelity of delivery of the adapted FB protocol. ***Secondary outcomes*** will include preliminary indicators of impact of the adapted FB protocol in improving HIV-related outcomes (eventual R01 primary outcomes) and MMT and mental health outcomes (eventual R01 secondary outcomes).

3.0 METHODOLOGY

AIM 1: Adaptation process: ADAPT-ITT. Our team has an established manual for FB, and procedures for adapting the FB manual for specific settings and contexts (e.g., our protocols for adapting for HIV, perinatal, and noncommunicable disease settings in our prior work in Malawi).[58,59] We will engage in a collaborative process with the full range of stakeholders who will use the manual to ensure contextual and patient relevance.

During the first 6 months of the project, we will follow the ADAPT-ITT model[60] to adapt the FB protocol for our population and outcomes. ADAPT-ITT consists of 8 steps (**Figure**). The first 2 steps, Assessment of needs of the patient population and Decision about the evidence-based intervention to select, as summarized in the Specific Aims and Significance sections, have guided the development of this proposal and the selection of FB to address CMDs among patients with HIV on MMT.

ADAPT-ITT Model Steps

1 Assess population needs
2 Decide on intervention
3 Adaptation with stakeholders
4 Production of adapted protocol
5 Topical expert input
6 Integration of expert input
7 Training
8 Testing of adapted protocol

Wingood et al.*JAIDS* 2008

Step 3 (Adaptation) involves presenting FB to members of the target population and soliciting responses, encompasses feedback from potential clients and counselors. We will present the FB protocol to 5 distinct groups: patients (in-depth individual interviews, n=16), family members of patients (in-depth individual interviews, n=16), HIV/MMT clinicians and staff (2 focus groups, n=10 total), and directors of HIV/MMT clinics (individual interviews, n=6). We will solicit their feedback through in-depth interviews and focus group discussions.

Specific inclusion criteria and study activities for each group:

- HIV/MMT patients (n=16): Patients receiving both HIV and MMT care, who also have elevated symptoms of depression, anxiety, or stress on the DASS-21: a depression subscale score ≥ 7, an anxiety subscale score ≥ 6, and/or a stress subscale score ≥ 10. These cut-offs indicate at least a moderate severity of symptomatology (see Trial Phase below). We will purposively sample participants to enroll at least 4 patients with depression, at least 4 with anxiety, and at least 4 with stress (one individual can help meet more than one of these targets if they are elevated on more than one domain). These individuals will complete one-time individual in-depth interviews lasting approximately one hour.
- Family members (n=16): We will ask each patient if we may speak with their spouse, mother, or other primary household caregiver. We will ask if they have disclosed their HIV and injection drug use status to that family member, and will only approach the family member if the patient has disclosed to them and is willing for us to talk with them about these issues. These individuals will complete one-time individual in-depth interviews lasting approximately one hour.
- HIV/MMT clinic providers and staff (2 focus groups, up to n=10 total): We will invite HIV/MMT clinic providers and staff who have meaningful involvement in the delivery of care for participating patients. These individuals will participate in a one-time focus group lasting approximately one and a half hours.
- HIV/MMT clinic directors (n=6): We will invite directors of the HIV/MMT clinics, CDC Hanoi, DOH Hanoi to complete individual interviews lasting approximately one hour.

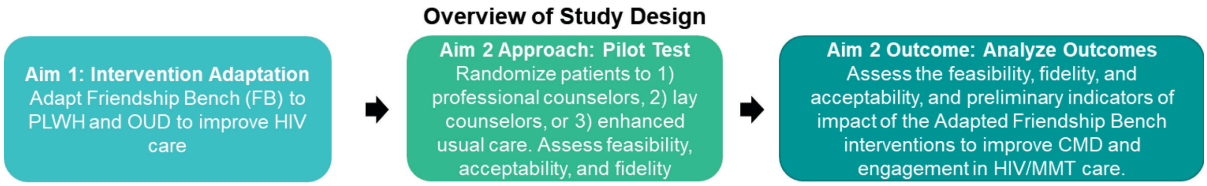
Data collection and storage. All in-depth interviews and focus group discussions will be audio-recorded, stored on a secure server, transcribed and translated for analysis.

In step 4 (Production), this patient and provider feedback will be incorporated into a first draft of the adapted FB protocol. Steps 5 and 6 involve solicitation and integration of topical expert input. We will identify three individuals external to the study team with expertise in FB and in behavioral interventions for people with HIV and/or OUD to review the adapted

protocol. Feedback from this review will inform the development of the next draft of the protocol. In steps 7 and 8, an interventionist will be trained and this second draft will be piloted with 5 eligible patients to further refine session content. The process will culminate with a final version of the adapted FB protocol that will be ready for formal evaluation in Aim 2 in a three-arm pilot study.

AIM 2: To assess the feasibility, fidelity, and acceptability of the adapted FB as well as preliminary indicators of its impact in improving CMD and engagement in HIV care and drug use treatment via a small three-arm individually randomized trial, comparing FB by professional counselors to FB by lay counselors to enhanced usual care for PLWH and OUD with CMDs.

Study Design. We will complete a pilot trial in which we will randomize 75 eligible patients to either the FB by a professional counselor (n=25), or FB by a lay counselor (n-25), or enhanced usual care (n=25). Patients will be enrolled from 4 MMT clinics under CDC Hanoi jurisdiction and with which we have previous successful collaborations. Patients meeting full eligibility criteria (see below) will be invited to provide written informed consent to participate in the study. As a pragmatic effectiveness trial, the purpose of the eventual R01 will be to compare the effectiveness of the adapted FB protocol delivered by a professional counselor and delivered by a lay counselor relative to enhanced usual care in improving HIV/MMT care engagement and outcomes (primary outcomes for the future trial).[61] Therefore in this pilot, consenting participants will be individually randomized in the same way, to one of those three arms (described below).

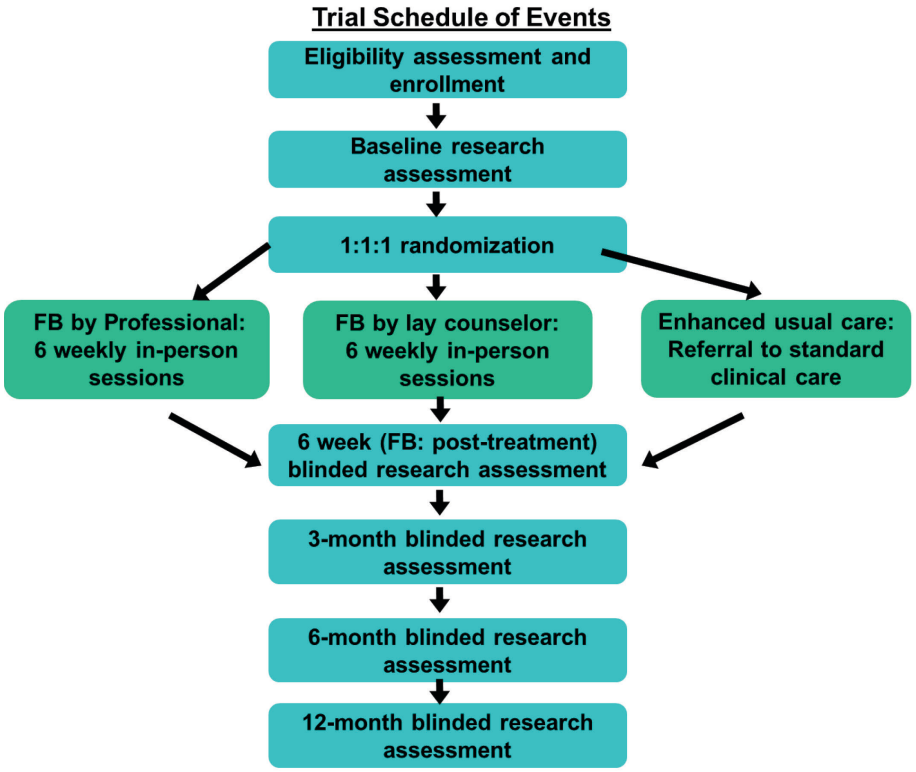


Study Procedures.

After enrollment but before randomization, enrolled participants will complete a baseline research assessment including:

- sociodemographic information;
- self-reported health;
- Although a full psychiatric diagnosis is not required for eligibility (see D.7.c above), enrolled participants will complete a diagnostic reference standard assessment, the Mini International Neurological Interview (MINI),[62] so as to fully characterize the prevalence of psychiatric diagnoses among this group with elevated symptoms

- To the standard MINI we will add additional questions regarding family history and course of illness to characterize severity of illness, a potential modifier;
- a urine drug screen;
- a systematic Time Line Follow Back past 30 days assessment of alcohol and other substance use;[63]
- and key related structural and psychosocial factors and potential mediators and moderators including housing stability, exposure to violence/intimate partner violence, coping, social support, and experiences of stigma related to mental health, substance use, and accessing mental health and substance use treatment.



Randomization: Participants will then be randomized 1:1:1 either to the adapted FB protocol delivered by a professional counselor, or to FB by a lay counselor, or to enhanced usual care (EUC). *Given the R34 focus on feasibility and acceptability, we will not stratify randomization by any factors; if we observe problematic imbalance, we will conduct adjusted analyses when comparing preliminary indicators of efficacy between arms.*

Enhanced usual care will include general training of the HIV providers and clinics about CMD identification and management, and feedback to the HIV provider of the status of their enrolled patient to allow follow-up per the clinic's standard care. We will collect information in follow-up interviews to characterize the care that patients receive. These activities will occur in all three arms, but they are the only activities in the EUC arm.

FB arms (by professional or lay counselor): Participants randomized to professional counseling or lay counseling will initiate FB with the trained counselor. Patients in these arms will receive 6 weekly counselling sessions per the adapted FB protocol (Aim 1).

Compensation: Per our prior standard in HIV/MMT counseling studies, clients will receive nominal compensation when attending each counseling session to offset transportation costs.

Research interviews: Participants in the enhanced usual care arm will complete a follow-up research assessment at 6 weeks post-baseline. Participants in the adapted FB arms will complete this assessment after the final FB session, also expected to be at approximately 6 weeks post-baseline. All participants will complete research assessments at 3, 6, and 12 months post-baseline. These follow-up assessments will assess the same domains as the baseline assessment and will specifically collect information on non-study psychiatric treatments in all arms, including both counseling and medications (both expected to be

extremely rare). Follow-up interviews will also repeat the MINI (all time points) to have a structured assessment of change in psychiatric diagnoses over time, as well as repeating the urine drug screen (6 months only) and Time Line Follow-Back alcohol and substance use assessment (all time points). Participants in all arms will receive standard financial compensation for their time after completing each research interview. All follow-up assessments will be conducted by trained research interviewers who are blinded to the participant's trial arm.

Health care provider eligibility: Health care providers will also provide feedback on use of the adapted protocol. These participants will include a total of 10 different HIV and MMT care providers employed at the study clinics. The HIV/MMT care providers will be a mix of clinic staff delivering the intervention, HIV support service providers and other care providers that are determined to have meaningful involvement in the delivery of care for participating patients. These provider participants will complete semi-structured interviews at baseline, 6-weeks post enrollment, and at 3 months, 6 months, and 12 months to provide feedback on feasibility and acceptability of the adapted FB protocol.

Outcomes, Measures and Data Collection. The ***primary outcomes*** of the pilot trial will be the feasibility, acceptability, and fidelity of delivery of the adapted FB protocol. ***Secondary outcomes*** will include preliminary indicators of impact of the adapted FB protocol in improving HIV-related outcomes (eventual R01 primary outcomes) and MMT and mental health outcomes (eventual R01 secondary outcomes).

Primary Outcomes: *Feasibility* will be defined as the ability to successfully enroll and retain PLWH and OUD with CMDs in the pilot intervention. Feasibility will be evaluated by measuring the recruitment rate (number of patients approached to accrue the final sample). Additional indicators of feasibility will include study retention, defined as the ability to retain PLWH and OUD with CMDs in the pilot trial. Study retention will be evaluated by measuring the number of participants retained in the study (number of patients enrolled at baseline who are still enrolled in the trial), through study completion. An additional measure of intervention feasibility will be defined as the number of FB sessions attended by participants out of total FB sessions offered during the target intervention duration of 6 weeks.

Acceptability will be defined as the ability to deliver a culturally and resource-appropriate intervention. Acceptability will be assessed through brief exit interviews with all patient participants (n=75), HIV providers treating patients in the FB protocol, professional counselors (n=3), lay counselors (n=3), and supervising Master Trainers (n=1 per clinic, n=2 or 3 total). Exit interviews with patients will occur after the final FB session, while exit interviews with other groups will occur after the end of FB activities at each site. Exit interviews will include both closed and open-ended questions and will assess how easy the intervention was to participate in or deliver, the perceived usefulness of the intervention, and suggestions for improvement. The primary measure of acceptability will be overall participant satisfaction defined by the number of patients who were either very satisfied or somewhat satisfied with the FB among all participants who received the FB. Satisfaction will be measured on a 4-point Likert scale-- 1 indicates high satisfaction and 4 indicates high dissatisfaction.

Fidelity will be defined as adherence to the intervention protocol. Fidelity to session content for individual counseling sessions will be assessed by a Master Trainer by using a checklist of counseling session elements either during direct monitoring or using audio recording of up to 3 randomly chosen sessions per counselor. As we have defined in prior work, meeting or exceeding expectations at least 75% of checklist items during each

session will be considered fidelity to the intervention protocol.

Secondary Outcomes: Secondary outcomes will be used to provide preliminary information about effectiveness, taking into consideration the limited sample size for the pilot project**.** *HIV-related outcomes* (the primary outcomes for the eventual full-scale trial) will be defined as (a) *viral suppression at 6 months*, and (b) HIV appointment adherence between baseline and 12 months of follow up. Viral load will be captured from clinical records, or ordered by the study if no viral load is collected in the appropriate window. HIV appointment attendance will be evaluated by measuring the proportion of scheduled visits in the 12-month follow-up period that are attended vs. no-shows (the "kept visit proportion"), with no show defined as no appointment kept in the 30 days following a scheduled appointment. HIV appointment data will be abstracted from clinic records at the end of the study period.

Mental health outcomes (the secondary outcomes for the eventual full-scale trial) will be defined as DASS-21 total score indicating any CMD symptoms as well as mean subgroup scores for depression, anxiety, and stress at 6 weeks after enrollment (FB: treatment exit) across all study arms. We will consider both the simple severity level at follow-up as well as the absolute reduction in symptoms from baseline.

Methadone maintenance engagement (another secondary outcome for the full trial) will be defined as the proportion of days with methadone maintenance therapy adherence measured from study baseline through 12 months of follow up.

Additional (tertiary) outcomes: Tertiary *HIV-related outcomes* will be defined as (a) viral suppression at 12 months and (b) consistent ART use over 12 months as confirmed by clinical records. Tertiary *mental health outcomes* will be defined as DASS-21 total score indicating any CMD symptoms as well as subgroup scores for depression, anxiety, and stress at 3 months, 6 months, and 12 months across all study arms. We will consider both the simple severity level at follow-up as well as the absolute reduction in symptoms from baseline.

3.1 Study Sites

The proposed study will be at conducted at 4 public MMT clinics in the Hanoi, Vietnam area where we have successfully enrolled patients in prior studies. Each of the 4 health centers provides methadone maintenance treatment (MMT) to individuals with opioid use disorder as well as integrated HIV/ART care to those additionally living with HIV. Male users make up the vast majority of individuals with opioid use disorder here. In Vietnam, PLWH and OUD typically get integrated treatment with ART and methadone at district health centers. Thus, the co-location of HIV and MMT services makes these health centers ideal locations to serve PLWH with OUD. CMD screening and assessment are rare to nonexistent at HIV/MMT clinics in Hanoi, as in most clinical settings in Vietnam.

UNC Project in Vietnam will serve as the administrative home for the study and has longstanding relationships with all 4 proposed study sites, the Ministry of Health, and CDC Hanoi. Approximately 80 individuals living with HIV and with OUD present monthly at each site, providing adequate numbers for aim 2. UNC Project has previously successfully recruited and enrolled PLWH on MMT

3.2 Population

Inclusion criteria

Eligible individuals will be adult patients (18 years and older) being treated at the MMT clinic

whose medical record indicates infection with HIV will be screened with the DASS-21,[64] which has been translated, standardized and validated in the Vietnamese population.[65,66] The DASS-21 assesses symptoms of depression, anxiety and stress among adults. The respondent is asked to think about their experiences in the past seven days and to rate each of the 21 items along a 4-point scale from 0 ("Did not apply to me at all–Never") to 3 ("Applied to me very much, or most of the time–Almost always"). There are three subscales, each with 7 items (DASS-21-Depression, DASS-21-Anxiety, and DASS-21-Stress) allowing calculation of three subgroup scores (0-21) and a total score (0-63). We then use these totals to identify the likelihood of a depressive disorder, an anxiety disorder, a stress-related disorder, or any of the three. Consistent with our prior work[67] and with prior validation studies in the Vietnamese population,[66] we will consider as eligible all patients with a depression subscale score ≥ 7, an anxiety subscale score ≥ 6, and/or a stress subscale score ≥ 10. These cut-offs indicate at least a moderate severity of symptomatology. Further, to ensure that we are identifying clinically meaningful CMDs rather than transient mood fluctuations, we will require that elevated depressive symptoms be present for ≥2 weeks and elevated anxiety or post-traumatic stress-related symptoms be present for ≥1 month. We will consider a positive screen for any of the three categories as indicating a CMD.

Exclusion criteria
Those with evidence of psychosis or bipolar disorder per the MINI will be excluded.

3.3 Duration

Aim 1 (protocol adaptation) will be conducted over a 9-month period in year 1 (July 2020 – March 2021). Aim 2 (pilot trial) will begin in the last 3 months of year 1 (April 2021) and has two parts: implementation of the pilot study with enrollment and 3 months of treatment sessions (April 2021 – December 2021) and ongoing assessment of key outcomes at 3, 6, and 12 months (through December 2022).

3.4 Sample Size

A total of 75 patients will be enrolled over time, recruited over a three-month period in year 2.

We recognize that the purpose of a pilot trial with limited sample size is not to be fully powered to detect statistically significant differences on patient outcomes but rather to provide reasonably precise estimates of parameters such as acceptability and fidelity, as well as preliminary evidence of the likely magnitude of effect of the intervention on the outcomes planned for the later trial. Assuming 80% retention (consistent with our team's previous work in this population), our starting sample size of 50 intervention participants is sufficient to estimate parameters such as the proportion of participants rating the intervention as acceptable with a 95% confidence interval of ±10-15 percentage points, and parameters such as the proportion of FB sessions with acceptable fidelity with a 95% CI of ±6-8 percentage points. Our starting sample size of 25 participants in each arm, with 80% retention, is sufficient to estimate risk ratios of the effect of the intervention on outcomes that have 95% CIs that are two- to three-fold wide (e.g., RR=0.63; 95%CI = 0.38-1.00 for the presence of elevated symptoms), depending on various assumptions about outcome frequency. For comparison of effect sizes, we note that the 24-clinic cluster-randomized trial of the FB found effect sizes much stronger than this (adjusted risk ratios of 0.21 [0.15-0.29] for presence of any symptoms and 0.28 [0.22-0.34] for presence of depressive symptoms). Thus the sample size is adequate to achieve our aims.

3.5 Data Sources

Sources of data for this study include the participant baseline and follow-up assessments, provider semi-structured interviews, audio recordings of counseling sessions that will be rated for fidelity, and medical record data (to collect HIV appointment attendance and viral loads). We will capture viral load from medical records when possible; if no viral load is scheduled at the requisite time point for the study, then the study will order and pay for a viral load test. Blood samples for study viral loads will be drawn by the same clinic staff and in the same manner as clinic-ordered viral loads

3.5.1 Record Availability

The site investigator will make all data abstraction documents and records readily available for inspection by the local IRB and the Office for Human Research Protections (OHRP) as requested.

4.0 ANALYSIS

Statistical Analysis. Feasibility, acceptability, and fidelity will be evaluated using descriptive statistics. We will compare mean fidelity scores between the professional FB and lay FB counselors using an intent-to-treat approach, using a robust variance estimator to account for multiple observations per counselor. Means and proportions for HIV-related and mental health outcomes will be compared between arms using an intent-to-treat analysis approach.

We will evaluate effectiveness measures comparing professional counselors to enhanced usual care and lay counselors to enhanced usual care. Considering the purpose of this small pilot trial, our focus will be on estimating effect size and precision rather than statistical significance and hypothesis testing. To take advantage of the repeated-measures nature of the outcome data, we will also fit generalized estimating equation (GEE) regression models, using a link appropriate for each outcome (i.e. identity link for continuous variables and log link for binary variables), to simultaneously examine differences in outcomes at 6 weeks, 3 months, 6 months and 12 months between the arms. Given the relatively small sample size, it is possible that important predictors of outcome (such as baseline mental health symptom severity or time in HIV care) could end up being unbalanced between arms; if this is the case we will conduct secondary regression analyses adjusting for the unbalanced potential confounder.

In **secondary analyses**, we will examine whether HIV-related, MMT, and mental health outcomes vary by proportion of FB sessions attended and by number of elevated symptom domains at baseline (depression, anxiety, and/or post-traumatic stress).

In **moderation analyses**, we will explore whether severity of illness (duration; symptom severity; family history) modifies any preliminary evidence of efficacy in primary outcomes, while recognizing that a pilot trial is not designed to be powered to statistically test modification hypotheses.

Missing data. Every effort will be made to minimize missing data, including collecting detailed locator information for the participant as well as for up to three individuals who could help reach the participant should they drop out of contact. However, some missing

data is likely to occur. We will examine the data for patterns of missingness (for example, are the patients with the greatest mental health symptom severity at baseline the most likely to be lost to follow-up?), and if identified, will conduct sensitivity analyses using inverse probability weights[68] to correct for the bias introduced by the missing data.

5.0 ETHICAL CONCERNS

5.1 Human Subjects

Safety considerations. Study staff will evaluate patients for safety who endorse any level of suicidal ideation whether or not they enroll in the trial. Safety assessment results will be conveyed to the clinical team as appropriate for further follow-up according to the clinic's standard operating procedures.

5.1.1 Institutional Review Board

Prior to implementation of this RCT, all protocol materials will be approved, as appropriate, by local institutional review boards (IRB)/ ethics committees (EC) responsible for oversight of the evaluation including the Hanoi Medical University Institutional Ethical Review Board and the Biomedical Institutional Review Board of the University of North Carolina at Chapel Hill. All research procedures will adhere to Vietnamese and US ethical standards for research involving human subjects.

5.1.2 Confidentiality, Risks, and Risk Minimization

Breach of confidentiality: There is always the possibility of a breach of confidentiality when conducting research. Disclosure of medical or other personal information about participants, particularly HIV, substance use disorder, and mental health status, may result in negative stigma being associated with the individual and/or family. Our research team is very aware of the need for absolute confidentiality and has extensive experience in dealing with highly sensitive personal medical and family information. While we acknowledge that a breach of confidentiality is possible, we anticipate that the likelihood is very low because of the precautions that will be taken to protect confidentiality. Research data will be coded (with identifiers removed). The linking file that connects the codes to individual identities will be securely stored by the study team. Research data will be stored securely on password-protected machines or servers or in locked cabinets, with access restricted to study staff.

For qualitative interviews: recording devices will be locked up when not in use, and audio files and transcripts will be stored securely on password-protected machines or servers with access restricted to study staff. Careful attention will be paid to anonymizing transcripts (removing potentially self-identifying references) and aggregating responses before sharing them with the full investigator team to prevent any potential for identification.

Risk of sense of coercion to participate: As addressed under 2(a) above, the informed consent process will emphasize that the provider is free to participate or not; a decision not to participate will have no negative impact on his or her employment, evaluation, or anything else related to the workplace; and the provider is free to end participation at any time. For patients, the informed consent process will emphasize that the patient is free to participate or not; a decision not to participate will have no negative impact on any aspect of his or her clinical care; and the patient is free to end participation at any time.

Patients may experience embarrassment or emotional distress during screening or as a result of talking about their mental health:It is possible that patients may experience distress when completing clinical symptom survey instruments or discussing their mental health. Based on our prior experience, we expect the degree of distress will be very limited. In case distress does occur, our training for study staff and clinicians will include sessions on identifying and responding to symptoms of distress. Empathy and sensitivity will be stressed in these trainings. The clinic's standard protocol for responding to distress during clinic encounters will be emphasized.

Patients may disclose suicidal ideation or intent to harm others, including a spouse or child: Patients may reveal suicidal intent or intent to harm others during study interviews or when discussing their mental health with their provider. We will have a thorough response plan in place. In general, response to severe depression, anxiety, stress, and suicidality will follow procedures standardized at the clinic site and appropriate to the situation. All suicidality reported during research contacts will be documented for clinician review. Participants with active moderate or high-risk suicidality will be evaluated by clinicians and referred for mental health follow-up per the clinic's standard protocol.

Patients may disclose safety concerns for themselves or others (e.g., victim of domestic violence or child is victim of abuse) during clinical care: Patients may disclose safety concerns for themselves or others (e.g., victim of domestic violence or child is victim of abuse) which will need to be addressed appropriately and with sensitivity. Such disclosure will be handled appropriately within the framework of existing legal mandates for reporting. The informed consent form will note that such information may require disclosure to law enforcement officials.

Health care providers: Risks to providers from this research include

(1) Risk of sense of coercion to participate

(2) Risk of breach of confidentiality of research data

Patients: Risks to patients from this research include

(1) Risk of sense of coercion to participate

(2) Risk of breach of confidentiality of research data

(3) Patients may experience embarrassment or emotional distress during screening or as a result of talking about their mental health;

(4) Patients may disclose suicidal ideation or intent to harm others, including a spouse or child;

(5) Patients may disclose safety concerns for themselves or others (e.g., victim of domestic violence or child is victim of abuse)

5.1.3 Benefits to Participants

This study has some minimal risks associated with participation and we anticipate that few participants will experience negative events as a result of taking part in the study. This research will improve our understanding of how a problem-solving mental health intervention can be adapted to people with HIV and opiate use disorder to improve psychiatric disorders and engagement in HIV care. In the long term, supporting PLWH and OUD that have co-occurring psychiatric conditions is expected to reduce psychiatric burden, improve engagement in HIV and MMT care, and ultimately improve CMDs and both HIV and MMT outcomes. Therefore, the risk to individual participants in our study is small relative to the potential benefit to be gained from the research.

5.1.4 Costs and Compensation

Study participants will receive standard compensation in line with CDC Hanoi practices for their enrollment visit and research outcome interviews.

5.1.5 Informed Consent

This protocol and the informed consent documents and any subsequent modifications will be reviewed and approved by the IRB and ethics committees responsible for oversight of the study. All procedures will conform to US and Vietnamese ethical standards regarding research involving human subjects.

Written informed consent will be obtained. Informed consent will clearly explain the purpose of the research, what will be required of the individual, and the risks and benefits of participation. All informed consent will be administered by study staff. For health care providers, the informed consent process will emphasize that the care provider is free to participate or not; a decision not to participate will have no negative impact on his or her employment, evaluation, or anything else related to the workplace; and the health care provider is free to end participation at any time. For patients, the informed consent process will emphasize that the patient is free to participate or not; a decision not to participate will have no negative impact on any aspect of his or her clinical care; and the patient is free to end participation at any time. Participants will be presented an informed consent form with the above information and contact information for the PI, study personnel, and IRB.

Patients will be approached for informed consent during clinical care appointments. Health care providers will be approached for informed consent during clinic working hours. In both cases, the informed consent process will take place in a private location in the clinic. Potential participants will be offered the opportunity to ask any questions they may have. Potential participants will have the opportunity to provide informed consent, decline to participate, or take additional time to consider participation (e.g. go home and return later).

5.2 Adverse Event Reporting

We do not anticipate any adverse events occurring given the nature of the minimal risks associated with this research. However, in the case that a breach of confidentiality does occur, the study team will immediately inform the IRBs.

- Deaths related to study participation shall be reported by the PI to NIDA and IRBs immediately and no later than within 5 business days of the PI first learning of the death
- Unexpected Serious Adverse Events related to study participation shall be reported by the PI to NIDA and IRBs within 10 business days of the study team becoming aware of the SAE
- Unanticipated Problems Involving Risks to Subjects or Others shall be reported by the PI to NIDA and IRBs within 10 business days of the study team becoming aware of the problem
- Adverse events and SAEs, including deaths, that are deemed expected and/or unrelated to the study shall be submitted in summary form to NIDA and IRBs with the annual progress report
- Protocol violations shall be submitted in summary form to NIDA and IRBs with the annual progress report

As a four-site pilot study, this project does not require a Data Safety Monitoring Board.

5.3 Study Discontinuation

The study may be discontinued at any time by the UNC IRB, the Hanoi Medical University Institutional Ethical Review Board, the Office for Human Research Protections (OHRP), or other government agencies as part of their duties to ensure that research participants are protected.

6.0 PUBLICATION AND DISSEMINATION OF RESEARCH FINDINGS

We will disseminate our results locally with stakeholders at the 4 clinics, our colleagues at Hanoi Medical University, our collaborators at CDC Hanoi, and any other interested parties (e.g. governmental representatives of other Southeast Asian countries, WHO representatives from the Southeast Asia Regional Office). We will also present results at national and international conferences (e.g., IAS, IAPAC). Abstracts presented at conferences will also be prepared for publication in suitable scientific journals to disseminate results to the wider scientific community.

Special considerations for clinical trials

We will ensure that our study is registered and results information is submitted to ClinicalTrials.gov, in compliance with all NIH policies. We will also ensure that informed consent forms used in the study include a specific statement about posting clinical trial information on ClinicalTrials.gov. Finally, we verify that the University of North Carolina at Chapel Hill, through its Office of Clinical Trials, has an internal policy in place to ensure that clinical trials registration and results reporting all occur in compliance with NIH policy requirements.

7.0 WORKPLAN

Timeline. The Friendship Bench adaptation will be completed in year 1 quarter 3. The pre-pilot RCT to test materials and study procedures will begin in year 1 quarter 4 and will last 3 months. The 3-arm pilot study will begin in year 2 quarter 1, with recruitment completed

within a 3-month period. Given that MMT/ART patients attend clinic daily for directly observed MMT, we anticipate little difficulty fully enrolling within a 3-month period. However, we have enough leeway in our timeline to extend enrollment if needed to achieve our target sample size. Treatment will be completed by the middle of year 2, while research follow-up through 12 months will be completed by the middle of year 3. Feasibility and fidelity assessment will be ongoing throughout the trial, while patient acceptability assessments will be folded into the research outcome interviews. The remainder of year 3 will focus on data analysis and dissemination, manuscript preparation, and planning for the follow-up R01 RCT. We expect to generate a minimum of 3 manuscripts from this pilot study.

Activity	Year 1				Year 2				Year 3			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
IRB Regulatory												
Aim 1 - Adaptation to improve CMDs and engagement in PWID with HIV												
Adapt Friendship Bench; feedback; finalize												
Aim 2 Approach - Pilot study of Friendship Bench in PWID with HIV												
Prepilot followed by 3-arm pilot study recruitment: 3 months												
Pilot study treatment sessions: ~3 months w/ follow-up through 12 months												
Aim 2 Outcomes- Assessment of feasibility, acceptability, fidelity, and preliminary indicators of impact												
Feasibility, acceptability, fidelity measurement												
Preliminary indicators of impact: Research interview at 3, 6, and 12 months												
Dissemination												
Data analysis and dissemination, manuscript preparation, RCT planning												

7.1 Project Management

This proposal is led by **Dr. Bradley Gaynes**, PI, Professor of Psychiatry and Director of the Division of Global Mental Health at UNC, who will provide overall administrative and scientific leadership in collaboration with the other co-investigators. He is supported in the US by **Dr. Brian Pence**, Professor of Epidemiology at the UNC School of Public Health, who will provide overall guidance on trial design and outcome measurement, and oversee intervention implementation and **Dr. Vivian Go**, Professor of Health Behavior at the UNC School of Public Health, will help adapt FB to PLWH on MMT, inform study design, and assist in collaboration with MOH and CDC Hanoi. The team further includes **Dr. Le Minh Giang**, Associate Professor and Chair of the Department of Global Health at Hanoi Medical University, who will assist with adapting FB to specific needs of HIV/MMT population in Vietnam and piloting the adapted protocol for testing in the proposed clinics in Vietnam; **Dr Viet Tran Ha**, Research Assistant Professor of Health Behavior at UNC and in-country Director of UNC Project-Vietnam, who will Monitor and direct in-country research activities; and **Drs. Dixon Chibanda**, Head of the Psychiatry Division at Harare Hospital, Zimbabwe, and **Dr. Ruth Verhey**, Senior Clinical Psychologist for the Friendship Bench Program, who both will consult on FB adaptation and development of supervision and fidelity systems, and help train the trainers.

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