Study Protocol

Official Title: Evaluation of the Efficacy and Mechanisms of a Novel intervention for Chronic Pain Tailored to People with HIV (STOMP)

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Study Coordinator: Alissa Eugeni

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I. STUDY OVERVIEW

Behavioral interventions for chronic pain among people living with HIV (PLWH) are an understudied area, with great potential to improve pain and function. Chronic pain is an important comorbidity that affects between 30% and 85% of PLWH and is associated with greater odds of functional impairment, increased emergency room utilization, suboptimal retention in HIV care, and failure to achieve virologic suppression. What is not known is how to optimally address chronic pain in this population. Opioids are a commonly used treatment for chronic pain, particularly in PLWH. Opioid prescribing for chronic pain often does not result in substantial improvement in outcomes and contributes to the growing epidemic of opioid addiction and overdose. In contrast, behavioral interventions are among the most effective and safest treatments for chronic pain in the general population. Pain Self-Management (PSM) is a Social Cognitive Theory (SCT)-based behavioral approach that involves pain-related skill acquisition and goal setting. PSM interventions have been promoted by the 2016 Department of Health and Human Services National Pain Strategy (DHHS NPS) as an effective, scalable approach to chronic pain management. Especially given the current opioid crisis, the DHHS NPS underscored the urgent need to develop and test PSM interventions tailored to the unique needs of vulnerable populations, particularly PLWH, that can be implemented and disseminated nationwide. Until an effective and scalable PSM intervention for chronic pain in PLWH is developed, reducing the burden of chronic pain safely and effectively in this population will not be possible.

II. OBJECTIVES

Our long-term goal is to significantly reduce the burden of chronic pain comorbidity in PLWH through the creation of an effective PSM intervention for HIV care settings. Our overall objective toward achieving that goal is to evaluate a novel theory-based PSM intervention, “Skills TO Manage Pain” (STOMP), that we developed for PLWH. We conducted a 44-participant, 2-arm randomized pilot trial of STOMP vs. usual care. Findings show that STOMP was feasible, acceptable, and showed preliminary evidence of impact on pain and function. Additionally, final analysis of STOMP’s cost/QALY was substantially lower than the $50,000 to $100,000/QALY benchmark often used to indicate cost-effectiveness. Although based on a pilot trial and, therefore, preliminary, these findings are promising, and suggest the importance of cost analyses in future STOMP trials.

For this study, we will accomplish our overall objective by focusing on the following primary specific aim: 1). Evaluate the efficacy of STOMP, a theory-based intervention tailored to improving chronic pain in PLWH. Given the rigorous intervention development process and promising pilot trial results, our working hypothesis is that STOMP will decrease pain severity and improve function in PLWH. We propose a two-arm randomized trial of STOMP vs. a usual care comparison condition (N=280).
We also propose the following secondary aims: 2). Conduct exploratory analyses of the impact of STOMP on HIV outcomes associated with chronic pain. Our working hypothesis is that STOMP will not only decrease pain severity and improve function, but increase retention in HIV primary care and virologic suppression rates. 3. Investigate proximal outcomes as potential mediators of STOMP’s impact on chronic pain. During our formative work, we incorporated the key SCT constructs of self-

efficacy, outcome expectations, and self-regulation into the intervention. Our working hypothesis is that these constructs are “proximal outcomes” through which the intervention’s impact on pain and function is mediated.

This study will be conducted at the University of Alabama at Birmingham (UAB) and the University of North Carolina at Chapel Hill (UNC), two sites within the Center for AIDS Research Network of Integrated Clinical Systems (CNICS) cohort. The University of Pittsburgh will serve as the lead site and will provide training and oversight.

III. STUDY ACTIVITIES

a) STUDY POPULATION

A total of 280 participants who are patients at UAB and UNC - enrolled in CNICS, experiencing chronic pain (Brief Chronic Pain Screening Questionnaire (BCPQ) = at least moderate pain for at least 3 months) and moderately severe and impairing chronic pain (PEG pain questionnaire = average of all three times is 4 or greater).

Inclusion Criteria

1. Enrolled in CNICS
2. Age ≥ 18 years
3. English-speaking
4. Chronic pain (Brief Chronic Pain Screening Questionnaire (BCPQ) = at least moderate pain for at least 3 months)

5. Moderately severe and impairing chronic pain (PEG pain questionnaire = average of all three items is 4 or greater)
6. Ability and willingness to attend the group sessions at the date/time specified
7. No plans for major surgery during the study period that would interfere with study procedures.

Exclusion Criteria

1. Do not speak or understand English
2. Are planning a new pain treatment like surgery
3. Cannot attend the group sessions
4. Had previously participated in the pilot study (STOMP)
5. Unwilling to provide informed consent

We will rely heavily on active recruitment using patients identified as having chronic pain on the BCPQ and PEG on CNICS pain Patient Reported Outcome measures. Additionally, participants will be recruited via word-of-mouth by clinic staff or providers, calls generated from flyer tear-offs and other advertisements placed in the clinic.

b) PRE-SCREENING (phone and then in-person)

Potential participants will be prescreened over the phone using our prescreening phone script once the participating site. A HIPAA waiver will be submitted with the initial submission. If the individual passes the telephone prescreen, he or she will be scheduled for an in-person pre-screening visit by a member of the STOMP recruitment team. The date and time of the pre-screening visit along with the participant contact information and

preferred method of contact will be recorded on the Prescreening Visit Appointment Form. Data from the pre-screening phone call and visit appointment forms will be transferred to a prescreening excel log for accurate tracking. About 48 hours prior to the in-person prescreen visit, a reminder call from the research staff will be made to remind the potential participant of the prescreening visit. If the research staff cannot locate the potential participant after three attempts, the staff will note an inactive status in the prescreening log.

On the day of the prescreen, the research staff member conducting the prescreen will log onto Redcap and establish a unique RedCap instance for this participant and complete the prescreen section only. Participants will be required to sign a prescreen consent form before the initiation of the session. At the end of the prescreen, the research staff member will record the participant's eligibility on the Prescreening Visit Appointment Form. If the participant is eligible for enrollment, a Screening and Enrollment Visit will be scheduled and recorded on a Screening and Enrollment Visit form. A separate excel log will collect data from the screening and enrollment visit form for tracking purposes. The participant will also be thanked and given their $25 incentive. If the participant is not eligible, he or she will also be thanked for their time and given a $25 incentive.

c) SCREENING AND ENROLLMENT

The Screening and Enrollment Visit will be scheduled approximately 2-4 weeks from the date of the pre-screen visit and recorded on a Screening and Enrollment Visit form. Participants will receive a reminder call at about a week and 48 hours prior to the

scheduled screening and enrollment visit. At the beginning of the screening and enrollment visit, the participant will complete the informed consent process, and then they will complete a baseline assessment.

Informed Consent Procedures

Informed consent will be administered by staff trained in accordance to the University of Pittsburgh, the University of Alabama at Birmingham and the University of North Carolina at Chapel Hill's Institutional Review Boards' guidelines for obtaining informed consent. The staff member obtaining consent must verify the following: protocol name, version number, dates for use, and institution. The Study team member will also ensure that the most recent informed consent is being used for the study. Initial informed consent must be completed and documented before any other study related procedures are done.

Comprehension will be assessed by asking the participant to summarize the study activities or some general open ended questions will be asked like what can you tell me about this study, can you tell me about how long the study may last, etc. The consent process is estimated to take around 30 minutes. Study staff will ensure that the participant has signed and dated the consent form including the HIPAA form. All signed consent forms will be stored in locked file cabinets under respective participant files.

Baseline Assessment

The research staff will then administer the baseline assessment which includes a confirmatory set of screening questions via RedCap. Confirmation of the participant's eligibility will be recorded in RedCap. If a participant is ineligible based on this RedCap assessment, they will be given a $50 incentive and thanked for their time, and they will

not be considered to have been enrolled in the study at any point (informed consent is asked before this point so that we can use any data generated in published findings). If a participant is eligible, they will also be thanked for coming and given their $50 incentive payment for their time. Completion of Baseline assessment will be recorded in excel logs.

RANDOMIZATION

Our team will utilize a 1:1 ratio for allocation to the STOMP intervention and Usual Care (UC) conditions. Our study statistician, Dr. Long, will use SAS to generate the randomization scheme stratified by whether the participant is on long-term opioid therapy (taking prescribed opioids for at least 3 months) and whether they have chronic multisite pain (pain in at least 3 locations or pain all over). Importantly, the PIs and outcomes assessors will be blinded to intervention vs. comparison allocation. Participants in the intervention and comparison conditions will have full access to all available clinical services at their respective sites.

d) INTERVENTION

The intervention group will receive “treatment as usual” plus the STOMP behavioral intervention. The “treatment as usual” refers to the standard of care that patients receive at the UAB and UNC clinics. This standard of care is for patients to discuss chronic pain with their providers at their discretion. Although highly variable, providers can recommend and prescribe pharmacologic (e.g., opioid and other pain medication), non-pharmacologic (e.g., physical therapy, referral to psychology) approaches for pain. This study will not interfere in any way with usual care.

The STOMP behavioral intervention consists of 12 intervention sessions (6 group and 6 individual sessions). The sessions will be completed over a period of 12-16 weeks from enrollment. The first intervention session will be a group session for all participants followed by individual and then alternating group and individual sessions for the rest of the intervention. The intervention group will utilize a study manual on pain management in which they will use with each session.

Group intervention Sessions

A total of 6 group sessions will be conducted over a period of 12-16 weeks from study enrollment date. These sessions will be led by a peer. A peer is an HIV-infected patient of the UAB or UNC clinics living with chronic pain and is a successful self-manager of his/her chronic pain. Peers will receive training that will include being a participant in all one-on-one sessions, and additional training to co-facilitate the six group sessions with the interventionist. Prior to the beginning of the first group session, participants will sign an Agreement of Confidentiality.

Participants will receive a reminder call/text approximately 48 hours before the group session to remind them of the upcoming session by the peer interventionist. If the participants cannot be reached on first contact, the peer interventionist will conduct up to three reminder calls or texts before the group session. Participants will also be notified of the upcoming group sessions at the end of each one-on-one intervention. Group sessions will be conducted in designated clinics at UAB and UNC. A sign-in sheet will be used to document attendance. Session notes will be used to document any major issues presented or any anecdotal nuances identified. The date, start time and end time of the

session will also be documented. Participants will complete an anonymous session feedback form at the end of each session. Each session will be audio recorded and transcribed later using a third party.

Individual Intervention Sessions

A total of 6 individual sessions will be conducted over a period of 12-16 weeks from study enrollment date.

Each individual intervention session will be scheduled by the staff interventionists preferably prior to next group session. The intervention date and time will be recorded on the Individual Intervention Session Form along with the intervention no. and topic. The participant will receive a reminder communication about the upcoming session approximately 48 hours before the session. An Intervention Session Form will be used to record the date, time, length of session, topic covered, homework, next steps, and any nuances identified during the session. An adverse event form will be completed if any physical, social or psychological issues arise a result of participating in this study and warrant immediate attention. The date of the next group session will be announced and the date of the next one-on-one session will be recorded at the bottom of the Intervention Session Form. Participants will complete a-session feedback form at the end of each session. Each session will be audio recorded. Selected sessions will be reviewed by a member of the research team not participating in the session for fidelity using the fidelity checklist (see Fidelity, below).

Reminder calls

Study staff will conduct up to 3 reminder calls to remind about their upcoming intervention session. Please note the purpose of these calls is to remind about appointments but in case patient initiates the conversation regarding intervention or other related to the study staff will talk to participant regarding intervention.

We will implement a series of best practices if a participant misses a session. This will include contacting the participant within a day of the missed session to schedule a make-up session in-person or by phone depending on the participant's preference; during that session, engaging in problem-solving as to why they missed the session and what barriers they envision going forward, and how those barriers might be addressed; and allowing participants to phone into group and individual sessions if needed. If there are things we can do to help that are reasonable (e.g., more reminders, more transportation assistance, or other things), we will provide them. Additionally, if they miss more than one visit, they may receive a call asking about their future participation in the study and whether, if they are unwilling to participate in intervention sessions, they would be willing to just complete outcome assessments.

Assessments

All participants in the intervention group will also receive a REDCAP assessment at baseline, post-intervention (0-month, after all sessions are completed), and then at 3, 6, 9 and 12 months post-intervention. The primary outcome will be at 3 months, and a 1-month window will be allowed after each timepoint for the patient to be contacted and assessed. An important medical event form will be administered to each participant at post-intervention (0-month) to screen for any unexpected medical incident, the severity of the event, its relation to the study, and medical follow-up. Viral load will also be

collected at baseline and at 12 months. At baseline, if a viral load from the prior 6 months is available in the medical record, that value will be recorded; otherwise, a viral load will be drawn. At 12 months, if a viral load in the prior 3 months is available in the medical record, that value will be recorded; otherwise, a viral load will be drawn. We will continue to conduct assessments every six months until the end of the study for all participants who complete the intervention by the beginning of Year 3. Participants who completed the baseline assessment by April 30, 2021 will continue to receive outcome assessments until April 2023 for a maximum of 41 months or 3 years. These assessments may be conducted by phone, if necessary, or in person. They will also participate in an audio-recorded in –person qualitative interview at the mid-point and end of the trial which will be transcribed using a third party company.

We will also investigate the intervention's impact on use of prescribed and non-prescribed opioids. Study staff will ask at each baseline and outcome assessment (0,3,6,9,12) the name of the participants' pharmacies along with the list of their current medications and dosage. Study staff will print out the medication lists and review it against the Opioid Medication Resource to identify the prescribed opioids. With written consent and a signed release of information from participants, a study staff member will contact the participants' pharmacy (or pharmacies) at the12- month assessment to verify the self-reported information provided by the participants in the prior assessments. The data will be added into an excel spreadsheet for collection and analysis. Participants will receive up to 3 reminder calls at about a week and 48 hours prior to the next outcome assessment.

Qualitative interviews

Participants assigned to intervention arm, peers and interventionists of the study will be interviewed at mid-point of the study and end of the study to provide their feedback on the STOMP intervention. These interviews will be audio-recorded and later transcribed using third party. Participants will be compensated $50 for each of the qualitative interviews.

e) COMPARISON CONDITION

The comparison group will receive "treatment as usual" as described above. The comparison group will also be provided with the intervention manual, however, no additional treatment will be provided to participants allocated to the control group.

Assessments

The comparison group participants will complete the post-intervention (0-month) follow-up at the same timing of the intervention group (12 - 16 weeks) after the 1st intervention session., and then will complete the outcome assessments (3,6,9,12) as the intervention group as described above including the baseline and the 12-month viral load assessments, and the important medical event screening at post-intervention. We will continue to conduct assessments every six months until the end of the study for all participants who complete the baseline assessment by the beginning of Year 3. Participants who completed the baseline assessment by April 30, 2021 will continue to

receive outcome assessments until April 2023 for a maximum of 41 months or 3 years. These assessments may be conducted by phone, if necessary, or in person.

We will also investigate the intervention's impact on use of prescribed and non-prescribed opioids. Study staff will ask at each outcome assessment (3,6,9,12) the name of the participants' pharmacies along with the list of their current medications and dosage. Study staff will print out the medication lists and review it against the Opioid Medication Resource to identify the prescribed opioids. With written consent and a signed release of information from participants, a study staff member will contact the participants' pharmacy (or pharmacies) at the12- month assessment to verify the self-reported information provided by the participants in the prior assessments. The data will be added into an excel spreadsheet for collection and analysis. Participants will receive up to 3 reminder calls at about a week and 48 hours prior to the next outcome assessment.

f) <u>PEER INTERVENTIONISTS</u>

As a peer interventionist, they will lead the intervention groups. Having peers facilitate the intervention groups fosters relationships with the participants since both groups share similar experiences. Peer interventionists will be compensated $500 for the initial training time and an additional $1,500 per the intervention block.

Each participating site will employ up to three peer interventionists for the group sessions. Peers should be living with HIV and be good pain self-managers. They must be mature, personable, highly responsible, with good communication skills and be able to follow rules of confidentiality. Potential peers may be identified by the

healthcare team or self-referrals and will be interviewed by research staff. They will not have contact with external institutions until officially hired.

During each 16 week cycle, one peer will serve as the lead interventionist and will co-facilitate (along with the staff interventionist) a group of ten participants; the other two (at sites when more than one peer is hired) will serve as first and second backup. The lead and first (active) back-up should attend all 6 group sessions. The second back-up will be utilized in the event a peer decides to drop out of the study. Determination of which two peers to start the intervention will be based on their scheduling preference. Research staff will conduct periodic check-ins to the active and (inactive) back-up to ensure he/she remains engaged in the study.

Peers will be responsible for the following activities.

<u>Lead peer</u>

1. Complete IRB and Good Clinical Practice certification
2. Participate in a 2 day STOMP training on pain self-management on an annual basis
3. Participate in 2 – 5 individual training sessions and 2 mock group sessions with staff intervention prior to start of intervention
4. Co-lead 6 one hour group sessions over a 12 - 16 week period for three years (arrive 30 minutes before and stay 30 minutes after) and attend weekly debriefing calls
5. Conduct reminder calls for the group sessions and provide phone-based peer support to intervention participants (as needed, during scheduled time)
6. Lead peer interventionist could work approximately 2 - 5 hours per week during each intervention cycle

<u>First Backup peer</u>

1. Complete IRB and Good Clinical Practice certification

2. Participate in a 2 day STOMP training on pain self-management on an annual basis

3. Participate in 2 – 5 individual training sessions and 2 mock group sessions with staff intervention prior to start of intervention
4. First back-ups will listen to and debrief about audio from group sessions as part of their continuous training which will occur monthly
5. Attend all 6 group sessions (arrive 30 minutes before and stay 30 minutes after)
6. First back-ups could work approximately 2 hour per week or less during each intervention cycle

Second Backup peer

1. Complete IRB and Good Clinical Practice certification
2. Participate in a 2 day STOMP training on pain self-management on an annual basis
3. Participate in 2 – 5 individual training sessions and 2 mock group sessions with staff intervention prior to start of intervention
4. Second back-ups will listen to and debrief about audio from group sessions as part of their continuous training which will occur twice during each 12 – 16 week period
5. Second back-ups could work approximately 1 hour per week or less during each intervention cycle

Payment Schedule

1. All peers will be compensated $500 for each annual 2 day STOMP training
2. The Lead peer will be paid $1,500 for each intervention period in which they serve as a lead
3. First and Second backup peers will be compensated at an hourly rate for study activities

RETENTION PROCEDURES

Several procedures will be implemented to optimize retention and ensure participant comfort while participating in both study arms. At all study visits, both intervention and follow-up, participants will be offered a beverage and snacks. In addition, for intervention group participants only, participants who are in need of transportation will be provided transit vouchers to attend intervention group and one-on-one sessions. (but not outcome assessments). In addition, we will have mid-study calls to confirm contact info in the UC group.

If a participant misses a session, study staff will contact the participant within one day of the missed session to schedule a make-up session either in-person or by phone based on the participant's preference. During the make-up session, study staff will engage in problem solving skills to address barriers that limited participant's attendance.

g) FIDELITY ASSESSMENTS

We will use a structured fidelity assessment tool developed by the study PI and psychologist consultant Dr. William Demonte. To assess one-on-one session fidelity across interventionists, time, and sites, we will audio record sessions. Initially, we will listen to and rate all one-on-one sessions. Once an interventionist completes five consecutive sessions with 80% fidelity, we will "certify" the interventionist as having the competence necessary to continue to conduct the intervention. Thereafter, a blinded assessor with intervention delivery experience trained by Dr. Demonte will review a 10% random sample. We will also provide ongoing supervision to prevent interventionist drift. We will monitor treatment receipt by using a checklist, which will capture whether

participants have used their tracking logs (which will be photocopied at each session by the staff interventionists). Given the less structured format of the group sessions, they will be assessed for knowledge sharing between the peers and participants and among participants, reflection on one-on-one session content, and fostering social support.

h) COLLECTION OF COST DATA

Each site will be responsible for tracking the following items in real-time: up-front training hours, cost of snacks, travel vouchers and participant manuals. Individual and group sessions will be tracked using the audio-record capability.

i) COLLECTION OF CNICS DATA

Center for AIDS Research Network of Integrated Clinical Systems (CNICS) Data:
CNICS data will be collected from abstractions from site medical record databases in collaboration with the CNICS data collection and patient reported outcomes infrastructure. Clinical and medical history data will include HIV viral load, CD4+ T-cell counts, co-morbid conditions, HIV primary care visit adherence, and medications. HIV primary care visit adherence will be extracted on all HIV care visits from the date of enrollment until the end of the study. Data from CNICS Patient Reported Outcomes (PRO) questionnaires including assessments of pain will be identified by study code and managed in accordance with CNICS electronic storage and data transfer guidelines.

j) TRACKING OF STUDY PATIENTS

Study staff will use the study's RedCap database to capture reminder calls, study visits, assessments, and intervention activities. Study staff will use excel logs to capture

prescreening, enrollment, randomization, timeline/window of outcome assessments, status of assessments, reminder call status for assessments and pharmacy data.. All study staff will be trained in Human Subjects Protections, and this data will be handled in accordance with CNICS electronic storage and data transfer guidelines.

Study staff will also review data entered in RedCap on a weekly basis as a quality assurance measure. The program manager at the University of Pittsburgh will provide oversight of data quality and will conduct monthly audits.

k) MANAGEMENT AND INTEGRATION OF UAB AND UNC SITES

Study PI Dr. Merlin and Program Director Alissa Eugeni will conduct regular in-person visits to each site. Additionally, there will be a weekly video Skype meeting with Dr. Merlin, Ms. Eugeni, and local study staff and site PIs at UAB and UNC. The purpose of these weekly meetings will be to track progress with study milestones, troubleshoot issues that may arise, and discuss any adverse events.

l) Assessment Table

STOMP

Data Collection Instrument	Pre-Baseline (1)	Baseline (2)	0 Month Post (3)	3 Month Post (4)	6 Month Post (5)	9 Month Post (6)	12 Month Post (7)	LT Assessment(s) (8)
SECTION I	X							
SECTION II		X						
SECTION III			X	X	X	X	X	X

SECTION IV		X	X	X	X	X	X	X
SECTION V		X	X	X	X	X	X	X
SECTION VI		X	X	X	X	X	X	X
SECTION VII			X					

m) <u>SNAP SHOT OF STUDY ACTIVITIES</u>

Procedure	**Length of Time Required of Participants**	**Frequency of Repetition**
Individual sessions (intervention group only)	6 sessions, up to approx. 60 minutes each	Maximum of on average every other week
Group sessions (intervention group only)	6 sessions, up to approx. 60 minutes each	Maximum of on average every other week
REDCAP assessments – see attached	Approx 30 minutes	Baseline, (0-month), 3,6,9 and 12 months after intervention, and every 6 months until the end of the study for all participants who

		complete the intervention by the start of Y3
Mid-study calls (comparison group)	Approx 5 min	8 weeks after the beginning of the intervention
Viral load assessment	Approx 15 minutes	Baseline and 12 month assessment visit
Qualitative interviews (peers, intervention group only)	Approx up to 120 minutes	After 6 sessions are completed and after all 12 sessions are completed
Pre-screen reminder calls	Approx 5 minutes	48 hours before pre-screening in-person visit
One-on-one and group reminder calls (peers, intervention group only)	Approx 5 minutes	Up to three reminder calls before the scheduled intervention date
Reminder calls at 0,3,6,9, 12 month-assessments, and every 6 months thereafter, if applicable	Approx 5 minutes	Up to three reminder calls,, 1 week prior to and 48 hours prior to scheduled assessment date.

n) SUMMARY OF COMPENSATION

Intervention group

In person for Prescreen	$25
Screening/Enrollment (Baseline) visit	$50
Mid-point qualitative interview	$50
End of study qualitative interview	$50
0, 3, 6, 9 and 12-month assessments	$50 each
Longer term assessments (18, 24, 30, 36,41)	$50 each
Control group	
In person for Prescreen	$25
Screening/Enrollment (Baseline) visit	$50
0, 3, 6, 9 and 12-month assessments	$50
Longer term assessments(18, 24, 30, 36,41)	$50 each

IV. DATA COLLECTION AND MANAGEMENT

All study documentation will be kept in locked file cabinets in in study personnel's offices at UAB and UNC. RedCap database can only be accessed by STOMP personnel using UAB and UNC computers or encrypted laptops.

V. DATA ANALYSIS

A separate document will be submitted by the PI of the study for the statistical analysis plan.

VI. CRISIS PROTOCOL

As a general note, referrals can be made for crisis consultation at any time. The research staff will document the findings of his/her evaluation and the course of action taken.

Providers for the patient may be informed about the same. If it becomes apparent during data collection that a patient is in danger, is suffering, or is at risk for developing a clinically relevant physical or mental health condition (e.g., depression, suicide, self-injurious behaviors), relevant staff in the local clinic (e.g., professional mental health counselors, social workers, and nurses/providers) will be notified and standard procedures already in places in each clinic for ensuring the physical and mental wee-being of patients will be followed (e.g., intervening and/or providing appropriate referral, as indicated).

VII. PROTECTION OF HUMAN SUBJECTS

Our team has devised a comprehensive plan for ensuring protection of human subjects throughout the course of the proposed study. We will utilize an English-language consent form with common phrasing that describes that no special privileges or considerations will be conferred as a result of study participation, and that access to medical care will not be affected by the potential participant's decision to enroll in the study. The procedures listed in the following sections detail procedures that have been approved and utilized during recent years of clinical and behavioral trials at each site for collaborative research that utilizes sensitive information from participants. Our team will make every effort to protect all participants' confidential and private information in order to minimize possible study-associated risks.

All findings related to this research will be available and provided to study participants in accordance with standard practices. Clinical and measurement data used for research studies will be released only in de-identified fashion.

In addition, all study personnel are required to renew Human Subjects trainings annually, or in accordance with their site regulatory mandates.

VIII. KEY PERSONNEL AND ROLES

Principal Investigators:

Jessie Merlin	Principal Investigator	University of Pittsburgh
Jane Liebschutz	Co-Investigator	University of Pittsburgh
Michael Saag	Co-Investigator	University of Alabama at Birmingham
Michael Mugavero	Co-Investigator	University of Alabama at Birmingham
Dustin Long	Co-Investigator	University of Alabama at Birmingham
Olivio Clay	Co-Investigator	University of Alabama at Birmingham
Sonia Napravnik	Co-Investigator	University of North Carolina at Chapel Hill
Amy Durr	Co-Investigator	University of North Carolina at Chapel Hill
Claire Farel	Co-Investigator	University of North Carolina at Chapel Hill

Research Team:

Bernadette Johnson	Program Director	University of Alabama at Birmingham
Tammi Thomas	Coordinator, Outcome Assessor, 2nd B/U Interventionist	University of Alabama at Birmingham
Kiko S. King	Interventionist	University of Alabama at Birmingham
Nashira Brown	1st B/U Interventionist	University of Alabama at Birmingham
Mark Butler	Recruiter	University of Alabama at Birmingham
D'Netria Jackson	Outcomes Assessor	University of Alabama at Birmingham
Alfredo Guzman	Informatics Director	University of Alabama at Birmingham
Satinder Kaur	Programmer	University of Alabama at Birmingham

Suneetha Thogaripally	Data Analyst	University of Alabama at Birmingham
Chastity McDavid	Qualitative Interviewer	University of Alabama at Birmingham
TBD	Research Staff	University of North Carolina at Chapel Hill
Kuo-Ping Li	Data Manager UNC	University of North Carolina at Chapel Hill
Alissa Eugeni	Project Manager	University of Pittsburgh

Statistical Analysis Plan

Study Design & Objectives. Our overall objective is to evaluate a novel theory-based PSM intervention, "Skills TO Manage Pain" (STOMP) developed for people with HIV (PWH). The design of the proposed study is a multicenter parallel-group individually randomized group clinical trial. The primate outcome is to evaluate the efficacy of STOMP, a theory-based intervention tailored to improving chronic pain in PWH immediately post intervention. The secondary outcomes are to investigate additional pain outcomes and proximal outcomes as potential mediators of STOMP's impact on chronic pain immediately post intervention and at 3 months.

The study will be conducted at 2 institutions in the United States (University of Alabama at Birmingham (UAB) and University of North Carolina at Chapel Hill (UNC)), and we will enroll adult patients, ages >18 years of age, consented to participate in the CFAR Network of Integrated Clinical Systems (CNICS), English-speaking, having at least moderate chronic pain, ability and willingness to attend the group sessions at the date/time specified, and no plans for major surgery during the study period that would interfere with study procedures.

The primary hypothesis is STOMP will decrease pain severity and improve function (as measured by BPI-total) in PWH. To test this hypothesis, we propose a two-arm randomized trial of STOMP vs. an enhanced usual care comparison condition. Our primary outcome will be Brief Pain Inventory (BPI)-Total score and will be measured at baseline and immediately post-intervention (~12 weeks after first intervention session). Our secondary outcomes will be changes in additional pain scales (PEG and BPI subscales of BPI-pain severity and BPI-interference), pain self-efficacy questionnaire (PSEQ), Patient Health Questionnaire (PHQ-8), and pain catastrophizing scale (PCS) between groups immediately post intervention. We will examine sustained differences in primary and secondary outcomes at 3 months post intervention.

Sample Size Calculation. Our primary outcome is the BPI-Total score as described above. Given that 20 participants progress through the study at a time, our total sample size should be divisible by 20. A sample size of 210 will provide 85% power to detect a difference of 1 on a 10 point scale with at standard deviation of 2.4 assuming a two-sample t-test with equal variance. The IMMPACT guidelines suggest that a change of 1 on the BPI is a minimum clinically significant difference. Additionally, the difference we found in our pilot trial was 1 (SD=2.4). Therefore, a sample size of 210 is sufficient to detect this effect size. To become divisible by 20 and allow for 25% dropout (slightly more than in the pilot trial) we will recruit 280 participants With our anticipated sample size, we will be able to estimate a margin-of-error of 1.5 percentage points for 95% intervals. For secondary outcomes, we can detect an effect size of 0.4, a medium effect, for continuous measures and a difference of proportions between 7.5% and 17% for binary measures, each with 85% power.

Interim & Final Analyses. We will not have any planned interim looks for stopping for efficacy, although safety and tolerability data will be monitored by the study DSMB at each meeting. The final analyses will be conducted once study follow-up is complete, after all data is

cleaned, and once the study database is locked. We anticipate database lock will happen by February 2024 with completion of primary analyses occurring by March of the same year.

Analysis Sets. The full analysis set will be based on an intention-to-treat (ITT) analysis with a per-protocol (PP) sensitivity analyses. The ITT analysis set will comprise all participants who have been randomized to either study arm, regardless of length of follow-up or actual intervention received.

Endpoint and Covariates

Our primary outcome will be the Brief Pain Inventory (BPI)-Total score, a commonly used composite measure of pain severity and the impact of pain on an individual's function. The BPI asks 11 questions about pain severity (pain at its worst, least, average, and right now) and the interference of pain in several aspects of patients' lives (activity, mood, walking ability, work, relations with other people, sleep, and enjoyment of life) on a scale of 0 (no pain/does not interfere) to 10 (pain as bad as you imagine/completely interferes). The BPI-Total score is the average score across all 11 questions.

There were no covariates included in our models, only time and treatment group indicator. We used linear mixed effects models which do not require adjustment for baseline as a fixed effect as it is included as an outcome. This allows for estimation of treatment effects at all follow-up times that takes into account any baseline differences between groups.

Handling of Missing Values. As a preventive measure, we will make every attempt to document all reasons for missing data. In addition, baseline characteristics will be compared between participants who do and do not withdraw from the study as a way to assess the impact of missing information and attrition. We will also compare the rates of lost-to-follow-up (LTF) between study arms.

Our general assumption will be that missing data is of the Missing at Random (MAR) mechanism. In this case, the use of linear mixed models for the primary analysis will be sufficient in reducing the impact that missing data has on biasing the primary results. Additionally, we will conduct a sensitivity analysis using multiple imputation via chained equations (MICE) to see how robust the overall inferences are.

Statistical Analyses.
The primary outcome – BPI-Total score – and the other secondary outcomes will be assessed as continuous variables. Linear mixed effects models will be performed to test differences between intervention and control conditions at the immediate post intervention and at 3 months. Models will include random effects for participant and therapy group. Therapy group is an identifier of the group of 20 that were randomized to create a STOMP group of 10. Fixed effects will be STOMP indicator, time and STOMP by time interaction. The primary hypothesis will be tested using the least squared means of each group at each time. We will check distributional

assumptions for these models using residual analysis including studentized residuals for individual observations, PRESS residuals which are composite residuals across an individual in longitudinal analysis, and Cook's distance. In compiling our analysis set, we will use an Intention to Treat (ITT) approach. We chose ITT for two reasons: 1) it fully exploits the benefits of balancing through randomization by including all patients who are randomized in the analysis; 2) it is a more "real-world" assessment of the intervention's impact as it allows for incomplete adherence and includes participants who may unintentionally cross over from the control to the intervention condition. Each of these issues can be handled well within the linear mixed models that will allow investigators to plot model-predicted trajectories for individuals with incomplete data. An additional advantage of linear mixed models is that they do not assume that the time between assessments is fixed and data for individuals who miss a time point can still be included. However, as this is the first efficacy trial to investigate STOMP, we will also conduct a per-protocol/as treated sensitivity analysis to understand the impact of the intervention without these complicating factors and adjust for differences by site. As a sensitivity analysis, missing data will be examined using multiple imputation methods. Specifically, multiple imputation using chained equations will be performed using previous baseline outcome data. Data will be imputed separately for each treatment group to improve efficiency and reduce bias in the treatment effect estimate.[1] Response to treatment defined by a reduction of at least 30% BPI Total score will be compared between groups using generalized linear mixed models with binary outcome using the same model effects and random components as the primary analysis.

Reference

1. Sullivan TR, White IR, Salter AB, Ryan P, Lee KJ. Should multiple imputation be the method of choice for handling missing data in randomized trials? *Stat Methods Med Res*. Sep 2018;27(9):2610-2626. doi:10.1177/0962280216683570