Evaluation of the efficacy and mechanisms of a novel intervention for chronic pain tailored to people living with HIV

STUDY PROTOCOL

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Send Questions or Comments to:
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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 California at San Diego (UCSD), two sites within the (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 UCSD - 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 California at San Diego'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 UCSD 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 UCSD 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. If the participants cannot be reached on first contact, research staff 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 UCSD. 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 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. Viral load will also be collected at baseline and at 12 months. 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 for the PI to review for 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. 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 for the PI to review for 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) PEER INTERVENTIONISTS

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 and an additional $1,500 per the intervention block.

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.

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.

Data will be extracted from the

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 UCSD 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 UCSD. The purpose of these weekly meetings will be to track progress with study milestones, troubleshoot issues that may arise, and discuss any adverse events.

I) 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) SNAP SHOT OF STUDY ACTIVITIES

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	48 hours before pre-screening in-

	minutes	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	$50
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 UCSD. RedCap database can only be accessed by STOMP personnel using UAB and UCSD 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.

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

Mallory Johnson	Co-Investigator	University of California at San Francisco
Edward Cachay	Co-Investigator	University of California at San Diego

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 California at San Diego
Huifang Quin	Data Manager UCSD	University of California at San Diego
Alissa Eugeni	Project Manager	University of Pittsburgh