Feasibility and acceptability of an adaptive treatment intervention for depression and engagement in HIV Care among Latinos living with HIV

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Principal Investigator: John A. Sauceda

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CONFIDENTIALITY STATEMENT

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Table of Contents

STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with applicable United States (US) Code of Federal Regulations (CFR), and the NIMH Terms and Conditions of Award. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the funding agency and documented approval from the Institutional Review Board (IRB), and if applicable, except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form(s) must be obtained before any participant is consented. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form(s) will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

INVESTIGATOR'S SIGNATURE

The signature below constitutes the approval of this protocol and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines, as described in the *Statement of Compliance* above.

Principal Investigator or Clinical Site Investigator:

Signed:  Date: 6.1.21

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Feasibility and acceptability of an adaptive treatment intervention for depression and engagement in HIV Care among Latinos living with HIV
Grant Number:	K01MH113475
Study Description:	This is the evaluation of the feasibility and acceptability of an adaptive intervention for depression and engagement in HIV care among Latinos living with HIV. The adaptive intervention is the sequencing of two low-risk behavioral interventions with text-messaging support. The focus of the study is on the sequencing of the interventions.
Objectives*:	Primary Objective: Feasibility of the intervention (i.e., execution of enrollment and intervention session completion rates). Secondary Objectives: Acceptability of the intervention (i.e., evaluation of engagement with intervention). Full details listed in the protocol.
Endpoints*:	Primary Endpoint: Half-way through active engagement with intervention (4 of 8 sessions completed) - this is the follow-up period dictating the sequencing decision. Secondary Endpoints: 12 weeks after enrollment - this is the final follow-up period.
Study Population:	A total of 45 Latino(a)/ Hispanic adult patients (18 or older) that are English or Spanish speaking, are living with HIV, report a mild level of depressive symptoms, and receive care at San Francisco General Hospital Ward 86.
Phase or Stage:	Not applicable
Description of Sites/Facilities Enrolling Participants:	Participants are recruited from Ward 86, at Zuckerberg San Francisco General Hospital in San Francisco, CA. This is a clinic setting with exam rooms, waiting room, and office space. Mission Hall is a research building at the Mission Bay Campus at U.C. San Francisco and includes private office and research study space.
Description of Study Intervention/Experimental Manipulation:	The interventions are behavioral activation therapy (BAT), cognitive-behavioral therapy (CBT) and text-messaging support. BAT is a 8-session one-on-one, in-person or video conferencing, intervention. CBT is an 11-session, one-on-one, in-person or video conferencing, intervention. Text-messaging support are one- and two-way SMS messages.
Study Duration*:	We expect a total of 12-months are needed to enroll 45 participants.
Participant Duration:	Participants are expected to be followed for 3 months.

1.2 SCHEMA

Flow Diagram - See Attached Figure of Sequential Multiple Assignment Randomized Trial Design.

1.3 SCHEDULE OF ACTIVITIES

	Pre-screening (Pre-consent)	Visit 1 Day 1	Visit 2 Day 7	Visit 3 Day 14 ±7	Visit 4 Day 21 ±7	Visit 5 Day 28 ±7	Visit 6 Day 35 ±7	Visit 7 Day 42 ±7	Visit 8 Day 49 ±7	Visit 9 Day 56 ±7	Visit 10 Day 63 ±7	Visit 11 Day 70 ±7	Final Visit Day 84 ±7
Screen for Eligibility	X												
Informed Consent		X											
Demographics		X											
Depression and Text-Message Criteria		X					X						
Outcome Evaluation													
Depression Ratings		X	X	X	X	X	X	X	X	X	X	X	X
Randomization		X		X									
1st Stage Intervention		X	X	X	X*	X*	X*[1]						
Primary Tailoring Variable - Decision Point on Sequencing				X									
2nd Stage Intervention					X	X	X*	X*	X*	X*	X*	X*	
Adverse Events Reporting		X	X	X	X	X	X	X	X	X	X	X	X

*Participants will all start with the first stage treatment - This is BAT with or without text-messaging support. After 3 of 5 sessions - approximately half-way through the intervention - their depression ratings are assessed that specifically inform the next course - This is called the second-stage treatment. Participants may either continue to complete the 5 sessions their first-stage treatment (i.e., BAT), get one extra booster session (denoted by *1), or switch to CBT, which includes up to 11 sessions (denoted by *).

2 INTRODUCTION

2.1 STUDY RATIONALE

Effective and efficacious treatments yield benefits to individuals, but the magnitude of those benefits is not equal in size. This study is attempting to understand how to optimize the benefits of efficacious treatments by building an adaptive treatment intervention using a Sequential Multiple Assignment Randomized Trial (SMART) design. The process of an adaptive intervention (i.e., specifically an Adaptive Treatment Strategy; ATS) is similar to the process of a medical diagnosis and treatment plan. A patient is diagnosed, a treatment is prescribed, and the patient is monitored. If a patient gets better, their treatment is maintained, if they get worse, a provider makes a decision to switch to a stronger treatment, hold off on a change, or add an additional treatment. Similarly, an ATS is a set of decision rules that dictate how to sequence treatments for depression; which are "adaptive" because they are not delivered uniformly to all patients. Instead, treatments are sequenced based on a patient's progress (e.g., get better, worse, non-adherent to treatment) before deciding the next course of action (i.e., maintain, augment or switch). Because the impact (i.e., efficacy) of an intervention is not the same for each patient, SMARTs individualize treatment interventions to optimize the efficacy that has already been demonstrated. We are evaluating the feasibility and acceptability of an ATS.

2.2 BACKGROUND

The official Significance section in the NIMH K01 Award is available upon request. Below is an abbreviated summary.

We have not adequately addressed HIV-related health disparities among Latinos in the U.S. In 2012, only 39% of Latinos diagnosed with HIV were estimated to have achieved viral suppression. In 2013, Latinos accounted for nearly 23% of new HIV diagnoses in the U.S., yet only made up 16% of the U.S. population (60% of Latinos newly diagnosed with HIV were foreign-born). Moreover, national HIV surveillance data showed that Latinos were less likely to be retained (at least 1 visit in the past year) or engaged in care (>2 visits 3 months apart in the past year) compared to Whites and African Americans. However, once retained in HIV care, Latino HIV outcomes improve and are equal to their White counterparts. Thus, the challenge is to develop a strategic response that overcomes the specific barriers to care affecting Latinos.

Mental health problems among Latinos living with HIV are pervasive. The most rigorous and nationally representative study to date found that up to 48% of people living with HIV (PLWH) met criteria for a depressive or anxiety disorder, which was primarily major depression (33%). Recently, similar estimates of depression were found in a diverse cohort of PLWH in the U.S. And while estimates of depression among HIV+ Latinos are as high as national estimates, they are crude because Latinos have only made a small percent of the study samples (< 15%) and must have been able to speak English. For context, nearly 1 in 3 Latinos in the U.S. are not proficient in English. Excluding Latinos from mental health studies based on language alone suggests we are missing key segments of the U.S. HIV epidemic.

To achieve sustained viral suppression and engagement in HIV care, we must identify and treat mental health problems. Depression is consistently associated with poorer ART adherence, poorer HIV care retention, worse HIV treatment outcomes, and faster mortality. Thus, the impact of the "Treatment as Prevention" strategy will be limited if depression impedes on the behaviors that lead to achieving and sustaining viral suppression. *And among Latinos, there is little use of mental health services for the treatment of depression*. For example, Latinos use general medical services at rates comparable to non-Latino Whites, but show less use of mental health services. And even when formally diagnosed with depression, Latinos (not specific to HIV) were less likely to access treatment compared to non-Latinos Whites; a result exacerbated for those living in poverty. In one systematic review, Latinos diagnosed with depression and prescribed antidepressant medication showed pervasive adherence problems. Therefore, poor depression treatment outcomes abound.

Cultural and language barriers are complex but need to be addressed in HIV and mental health research. Lower use of mental health services suggest that Latinos may have difficulty recognizing and/or reporting depressive symptoms because of language difficulties (i.e., poor communication with providers, inability to relay psychological distress) or cultural reasons (i.e., attitudes towards mental health, psychotherapy and psychotropic treatment beliefs, familiarity with psychotherapy). Other cultural barriers to HIV and mental health care include concepts of mental illness, treatment readiness, and integration with the health care system. And since Spanish-speaking Latinos have also been underrepresented in trials to test interventions' efficacy, use of "culturally blind" interventions for depression may have low acceptance and efficacy. Ongoing disparities in HIV, and in access and use of mental health services, make clear that the current health systems and approaches are inadequately suited to make strides in improving the health of HIV+ Latinos with depression.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

1. Breaches of confidentiality.
2. Inconvenience to the participant.
3. Intervention does not relieve depression symptoms in participant.
4. Mood changes - Participant experiences greater depressive symptoms during the course of the study.

2.3.2 KNOWN POTENTIAL BENEFITS

1. No direct benefits are guaranteed.
2. Data can help researchers learn how to treat and manage depression.
3. Given the evidence-base and designation of interventions as effective, we expect depression to improve, but this cannot be guaranteed nor the primary outcome of the study.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The risks involved in participation in the pilot study include learning that participants may have a mild severity level of depression, and if enrolled, the possibility that the interventions may not work, which may lead participants to feel discouraged, upset or hopeless (i.e., worse depression ratings). There is a

risk that they may feel some discomfort in talking about their feelings of sadness and maladaptive behaviors they have developed. As always, there is a risk for a loss of privacy if others learn they are participating in a study for depression. As described above, we have carefully developed all treatment protocols to ensure all risk are minimized and find no reason to believe any physical risks are present. Even if the potential risks were to occur we do not judge them to be grave or likely to affect the long-term mental health of the participant. The potential benefits include immediate reductions in the number and severity of depressive symptoms. Given the difficulties of being fully engaged in HIV care, the risks to participate described are reasonable given a need to address depression in a minority group disproportionately impacted by HIV and that ranks at the bottom among groups that have access to or benefit from mental health treatment programs.

3 OBJECTIVES AND ENDPOINTS

The primary objective is feasibility, which is defined as the measures "to determine whether an intervention [pilot SMART] is appropriate for further testing [and] to enable researchers to assess whether or not the ideas and findings can be shaped to be relevant and sustainable." The secondary objective is acceptability, defined as the tolerability or appropriateness of the SMART being studied from participant and clinician perspectives.

4 STUDY DESIGN

4.1 OVERALL DESIGN

The study design is a pilot sequential multiple assignment randomized trial (SMART).

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

No one treatment intervention equally benefits all persons. Thus, personalized/adaptive interventions may be one way to optimize the benefits people receive from treatment interventions. The goal of a pilot SMART is to yield feasibility and acceptability outcomes. These outcomes justify the decision rules that guided whether, when and how the intervention components (i.e., BAT, CBT and the text-messaging support) are adapted to a patient and informs the future full-scale SMART. It should also be noted that pilot SMARTs do not test the clinical impact of the interventions, which is already established. Pilot SMARTs optimize an intervention's efficacy by identifying how to best to sequence them.

4.3 JUSTIFICATION FOR INTERVENTION

The PI was a co-author of the first CBT intervention for Latinos living with HIV. In this study, there were improvements in self-reported depression and medication adherence, but a large portion of participants failed to complete all sessions, and weekly homework completion rates were also low. These limitations led to the current study, which focuses on starting individuals with a brief intervention first, and then supporting homework completion with text-message support.

4.4 END-OF-STUDY DEFINITION

The end of the study is defined by the feasibility and acceptability outcome timelines. We expect the full study to be completed in 3 months.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

Inclusion criteria include:

- HIV positive
- 18 years of age and older
- Self identifies as Latino/Hispanic
- Speak English or Spanish
- Receives HIV care at Ward 86
- Screened in with at least mild depression severity score to start (Patient Health Questionnaire-9 score >3; PHQ)
- Agrees to discuss depression, treatment preferences, and mobile health
- Owns a mobile phone that can send/receive short-message service (SMS) text messages
- Agrees to participate in the intervention that lasts three months
- Agrees to have medical and clinical data abstracted
- Able and willing to consent to participate

5.2 EXCLUSION CRITERIA

Exclusion criteria include:

- Not HIV positive
- Under 18 years of age
- Screened as having normal (PHQ-9 score of <2) or severe depression rating score (PHQ-9 score of 20 or higher).
- Does not self-identify as Latino/Hispanic
- Does not speak English or Spanish
- Does not receive HIV care at Ward 86
- Does not agree to discuss depression, treatment preferences, and mobile health
- Does not owns a mobile phone that can send/receive short-message service (SMS) text messages
- Does not agree to participate in the intervention that lasts three months
- Does not agree to have medical and clinical data abstracted one year after baseline
- Not able and willing to consent to participate

5.3 LIFESTYLE CONSIDERATIONS

There are no lifestyle considerations that are expected to affect the ability of a person to enroll who also meets all inclusion criteria.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in this study but are not subsequently assigned to the study intervention or entered in the study. Our study team is not going to reach out to individuals who do not meet the criteria for participation in this trial (screen failure) because of meeting one or more exclusion criteria that are likely to change over time. Screen failures are documented in the patient demographic data file at screening.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

All participants will be recruited from the Salud Clinic and Women's Clinic (housed within the Ward 86 HIV clinic at SFGH). Protection of the Latino clientele is a priority and informs the recruitment and screening process. Because the Salud Clinic specifically serves monolingual and bilingual Latino clients, Spanish-language services are easily accessible and nearly all providers and staff members are bilingual, including the PI of this K01 (Dr. Sauceda) and the Salud Clinic Director (Dr. Carina Marquez). All recruitment processes will be in full collaboration with Dr. Marquez and the Ward 86 Medical Director (Dr. Monica Gandhi) and take place during Salud Clinic and Women's Clinic hours.

Dr. Sauceda is in regular contact with Dr. Marquez and always ensure the privacy and protection of patients and that all services go uninterrupted. Therefore, all communication with patients will occur before or after their appointment.

Our proposed recruit plan is based on the experience of conducting two previous studies with the same population at the study site, and after many discussions with clinic staff and the clinic direct.

Our process first begins with presentations about our study at the Salud Clinic monthly staff meetings. We will present on our scheduling plan and re-introduce the inclusion and exclusion criteria. This is to inform the study staff and providers that we are actively recruiting patients. The Salud Clinic staff and providers assign their patients to a panel, and thus, are familiar and discuss the circumstances of each patient and their care. The clinic director, Dr. Marquez, prefers that all staff are aware of the studies that are currently enrolling participants so that if that they can make informal assessments if their patients generally fits the inclusion criteria. At monthly clinic meetings, we announce that we are recruiting from the waiting room on a set schedule and they can are free to walk over or refer patients to our clinical coordinator who can introduce the study. Importantly, no participants are ever enrolled the same day they are greeted or referred to us in the waiting room.

For direct referrals, we attend the Salud and Women's Clinic services, which start each Wednesday at 1:30PM. At 1PM, our clinical coordinator sets up in the waiting room and greets each staff member and provider, reminding them they are going to be in the waiting room. After each appointment, a provider or staff may choose to walk over any patients that are interested to our clinical coordinator in the waiting room who can assess their pre-eligibility (i.e., assess if interested in learning more about the study and exchanging contact information). Again, participants are never consented the day they are greeted. Further, there are also no incentives for providers or staff to recruit patients into our study, thus, patients should not feel coerced into seeking to participate. The Salud clinic staff prefer this method of outreach because it minimizes disruptions in clinic service provision as all contact happens after or in-between appointment activities.

For self-referrals, we will post flyers in the waiting room and the exam rooms. Typically, when a patient shows interest in the study, they will call or text our study phone line. At this point, the eligible

participant will be directly contacted within the week (i.e., delayed recruitment) to re-introduce the study, review and confirm the eligibility criteria, and schedule a day to begin the informed consent process (described below). Because participants will be recruited at their HIV care site, we have purposefully selected this delayed recruitment strategy to reduce any coercion to participate at the time they are introduced to the study. All communication and materials will be available in Spanish and English.

At the onset of the COVID-19 outbreak in March 2020, the research staff faced a significant challenge accessing the clinic premises. To address this challenge, research staff relied on doctor referrals and self-referrals to recruit participants. We will also add review of medical records of patients at the study site who may be eligible to participate and reach out to them at study visits.

Retention - The pilot SMART will require participants be followed over a three-month period. One of the benefits of the formative work that was completed for this project is that test ran the communication plans to increase the likelihood that the participant views the intervention and the study staff favorably, which will increase the likelihood of being retained over the follow-up period.

At the baseline interview, all participants will be asked to complete a locator form, which includes the listing of a current home address, phone number, and text or email information (if available), and preferences for how they would like to be contacted. The locator form also requests the names of three persons who they agree can be contact in the event they cannot be reached. The locator form also includes information we are allowed to relay over the phone or email (e.g., a participant may not mind that we state this is a call from the “Salud or Women’s Clinic” whereas another participant might prefer we state “UCSF”).

For subsequent appointments, each participant is sent a text-message and asked to confirm their next appointment. If they do not respond to the text-message within 24 hours, a second text-message is sent. Lastly, if the first two text-messages are not responded to, then a phone call is placed the following day. After three attempts, we make no additional outreach as to not burden the participant. Instead, we discuss communication efforts during the next face-to-face session. For participants randomized to the text-message tool, we have preliminary scheduled one-way text-message reminders to also be sent prior to their appointment. All participants have the option to reschedule if needed. If a participant misses a study appointment, they will be contacted to reschedule within 48 hours. A total of three attempts will be made to reschedule a missed appointment and we will make note of the reason for the missed appointment if provided. At each appointment a participant does attend, we will review their residence and contact information to ensure it is up to date and resolve any issues regarding future work or travel schedules should they arise. Additionally, all patients will have a monthly check-in call to verify their current home address and information and answer any questions about their participation. Given this comprehensive approach, we anticipate at least an 90% retention rate and have oversampled to ensure we have enough participants. All participants will be reimbursed with $30 per session to cover all costs related to travel, and effort. We feel this reimbursement amount is not coercive and is necessary when adjusting for the high cost of living in the San Francisco Bay Area of California.

6 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S)

6.1 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION OR EXPERIMENTAL MANIPULATION DESCRIPTION

The intervention activities are peer-reviewed and published manualized non-invasive programs that are based on psychoeducation principles, cognitive theory, and behavioral theory for depression. **They are featured in Simoni, Wiebe, Sauceda (PI), et al., 2013,** and from the manual titled ***CBT for Depression and Adherence in Individuals with Chronic Illness: Client and Therapist Workbook*, Oxford University Press, 2007**.

The intervention is comprised of three psychological theories to improving depression:

1. **Psychoeducation** is a standard educational approach to inform patients about the foundations of depression (i.e, what it is, what it looks like, how it affects people), and provides them with general knowledge around how to cope with and self-manage it. It is the foundation of behavioral therapy and cognitive-behavioral therapy.

2. **Behavioral therapy** attempts to improve a person's depressed mood by helping them to plan to engage in social activities or activities associated with mastery. When one engages in social or physical activities, they are inherently learning to associate the activity with feelings of elevated mood, thus, reinforcing them to continue to engage in the activity. The goal of the brief intervention is to help patients systematically plan to be more active and social, and to track how these activities are associated with changes in mood. Cognitive-behavioral therapy takes it one step further, but all patients first start with the behavioral therapy component first. For this reason, we are starting with assignment to what is known as behavioral activation therapy (BAT) - a brief behavioral therapy.

3. **Cognitive therapy** attempts to improve a person's depressed mood by teaching them that how a person feels and behaves is a function of how they think about themselves and the world around them. The key feature of depression in cognitive theory is negative thinking. To remedy negative thinking requires specific skills to learn how to monitor one's thoughts, and then to use strategies to think more adaptively to counteract the negative thinking. In cognitive therapy, by changing thoughts you change behavior and emotions. Cognitive theory requires more time and is a higher-order approach, which is why all participants are not starting with it. The cognitive component in "cognitive-behavioral" therapy typically comes later on in the program after the behavioral component has been learned. For this reason, we are only randomizing participants to receive this more time-intense program if the behavioral therapy is not sufficient to change depression ratings.

Participants in this study will be HIV+ Latino/as receiving care at the Ward 86 Salud or Women's Clinic, a Latino-serving HIV clinic at ZSFG. The SMART trial has three components: 1) brief, Behavioral Activation Therapy (BAT) 2) cognitive-behavioral therapy (CBT), and a text-messaging tool (mHealth).

- Delivery Method-Texts and interventions sessions will be completed either in person or via secure video chat platforms hosted by UCSF (i.e., HIPAA-compliant Zoom Video Conference platform). All text-messages are sent on secured encrypted UCSF Apple iPhones and with text-message platforms, such as Signal or Mosio.
- Session Length- Each session will ideally last 50-60 minutes.

- Intro Session- The study counselor will meet with the participant individually to complete a brief assessment and to identify topics to address during the counseling sessions. The counselor and the participant will discuss pressing issues, ongoing concerns, and areas identified as priorities by the participant.

1. BAT is a brief, 8-session manualized intervention that teaches participants about depression, how depression affects one's behavior (activities) and vice versa - this is the psychoeducation feature. Then, the focus of the remainder of sessions are on an action plan to identify new activities, schedule new activities, evaluate their development, and how to overcome barriers to engaging in new activities. For example, BAT would help a patient who states they feel isolated learn to understand how depression reduces energy, which is why they may not feel motivated to start their day. It would then help the patient create a plan to systematically schedule social activities (e.g., calling a friend to chat), how to make a plan for overcoming not feeling motivated, and then have them self-monitor their activities and evaluate their own progress.

Materials: Paper and pencil, calendars and monitoring forms, and mood rating scales. All documentation is stored in secured filing cabinets in badge-access only UCSF offices.

- **Session 1 (Building Trust and Introduction to BAT)** Introduce psycho-education about depression, the BAT rationale, daily monitoring forms and importance of engagement in HIV care.
- **Session 2 & 3 (Review and Introduce "High" value activities; Barriers to BAT):** Review Session 1 and introduce “high value” activity domains (i.e., activities key to relationships, mind- body health, spirituality, and daily life), discuss barriers to activities and monitoring (e.g., rumination as a “covert” maladaptive behaviors), and social “contracts” to engage network members (e.g., family) with scheduled activities, and discuss engagement in HIV care.
- **Session 4 & 5 (Review Progress, Challenges, & Maintenance Strategies):** Review Sessions 2-3, BAT rational and gains, maintenance strategies and adherence to BAT post-intervention (e.g., rank activities by difficulty or according to daily schedule), discuss communication with providers and the importance of engagement in HIV care.

Materials: Paper and pencil, calendars and monitoring forms, and mood rating scales. All documentation is stored in secured filing cabinets in badge-access only UCSF offices.

2. CBT combines BAT with cognitive therapy. CBT goes a step further in stating that negative thinking also affects behavior and emotions, and vice versa. It teaches patients how to "think about negative thinking," creates a plan to monitor their negative thoughts, and how to use specific strategies to think more adaptively. For example, a key feature of depression is use of cognitive distortions. In this example, patients may have the habit of using the distortion of "all-or-none" thinking, where if they feel they are not perfect then they have negative evaluations of themselves, rather than thinking more realistically that perfection is likely unattainable and that not reaching perfection does not equate to failure. In CBT, there are specific action plans to monitor how changes in thinking change are leading to changes in feelings and behaviors. CBT requires more time and more contact with an interventionist. Thus, we are starting with BAT and only sequencing CBT when patients are deemed to need it.

- **Session 1 (Building upon BAT & Introduce CBT Rationale):** Review principles of BAT and psychoeducation about the cognitive component in CBT.
- **Session 2-4 (Cognitive Restructuring):** Introduce how to monitor negative thoughts, record thought patterns, learn to identify new strategies for managing negative thoughts.
- **Session 4-6 (Problem-Solving):** Review previous sessions and discuss barriers to activities and thought monitoring, and barriers to completing the activities discussed in the intervention.
- **Session 7-8 (Relaxation Training & Maintenance):** Discuss the rationale of progressive muscle relaxation and how negative thoughts and feelings can start from physical arousal. Introduce monitoring forms and strategies to practice relaxation plans.

Participants will be identified as eligible by clinic staff or our research team (ZSFG staff prefer a flexible approach), complete the informed consent process, and then randomized to either:
(A1) BAT alone or (A2) BAT & mHealth text-messaging.

Participants randomized to (A1) BAT alone will complete a total of five, 1-hour sessions of behavioral activation therapy with a trained bi-lingual interventionist every two weeks. This intervention is publically available and manualized already. (Our prior work has shown that the intervention can be delivered by a wide-range of clinic and research personnel, not just mental health professionals; Simoni et al., 2013).

Conversely, participants randomized to the (A2) BAT & text-message support will receive an identical BAT program with the addition of one and two-way personalized text messages that will be delivered twice a week to facilitate engagement with the intervention activities.

Text-Messages - One-way messages will be sent as appointment and BAT adherence reminders (e.g., "Please remember to fill out your social activity planner?", while two-way text messages will be sent as "check-ins" with participants in the form of a mobile interventionist (e.g., "How is your activity planning going? If you need assistance, I can remind you of what activities you said you could do"). Participants will be asked to respond to these two way-text messages at their earliest convenience.

After three sessions of the five planned sessions have been completed, an assessment of the participants depression will be made using a cutoff score on the Patient Health Questionnaire-9 (PHQ-9), a self-reported rating scale for depression (this is called a “primary tailoring variable”). This primary tailoring variable will dictate the second sequence. Based on their PHQ-9 score, participants are coded as a “responder” or “non-responder;” a code that dictates whether their initial randomization assignment is 1) maintained, 2) augmented, or 3) switched to a second component (this is the second randomization and "adaptive" component).

Participants who were randomized to BAT alone and were coded as "non-responders" will be randomized to: 1. additionally receive text-message support, or 2. switched to receive CBT & text-message support. If switched to CBT & text-message support, participants will complete a total of eight intervention sessions that can be re-arranged to fit patient needs. CBT sessions will be scheduled once a week for 60 minutes (as described above, CBT integrates cognitive theory principles with behavioral theory principles, and thus, is more intensive). If participants randomized to BAT alone during their first stage of treatment and responded, they continue with maintenance of their BAT sessions.

Participants who were randomized to BAT & text-message support and were coded as "non-responders" will be randomized to: 3. augment BAT & text-message support treatment in the form of an extra booster session, or 4. similarly switched to receive CBT and text-message support. If participants who were randomized to BAT & text-message were coded as "responders", they will continue with maintenance of their BAT & text-message support sessions.

Participants will be asked to attend intervention sessions, respond to text messages, and participate in post-intervention exit interviews. Research team staff will be responsible for recruiting eligible participants to the study, coordinating intervention sessions (including reimbursements), and coordinating the text-message support component. Bilingual and English-speaking licensed clinical psychologists will supervise the conduct of the interventions and discuss updates during weekly and bi-weekly meetings.

Text-Messaging Protocol - One-way messages will be sent as appointment and BAT adherence reminders. Two-way messages will be sent during the protected time for "check-ins" with participants in the form of a "mobile therapist."

Security - All phones are reviewed and encrypted by the UCSF IT service desk and Mission Hall on the Mission Bay Campus and meet the UCSF Minimum Security Standards for Electronic Information Resources. The protocol for text-messages will be explained and demonstrations will be conducted in the first session to ensure participants comprehend the rationale. All study phone hardware, authentication of hardware (log-in credentials), and transmission networks (cellular-data networks, Wi-Fi) of patient health information will be protected through encryption software. We will show participants how to modify their phone settings and install free applications (e.g., Signal, TigerText) to encrypt the text-messages or have them delivered in discreet form (e.g., content not to appear on home screen).

Data Collection - All study phones will store text-message communication and will be downloaded from the smart phone into a Microsoft Word document. From this document, all responses are then pasted into a secure and password protected Microsoft Excel file. The excel file lists all participant unique ID numbers, message history, and schedule preferences. The file is stored on the UCSF Box cloud storage.

One-way Messages - One-way messages require no confirmation of receipt and are for the purposes of reminders. For example, for appointment reminders (in English), we will send the following reminder tailored to the participant - "*Hi Lorena, this is Dr. Sauceda reminding you of your appointment on Monday, June 1st at 11:30AM at the Salud or Women's Clinic. To cancel or reschedule, please call or text the study phone line @415-476-6045*." For a reminder to adhere to the intervention activities, we will send the following - "*Hi Lorena, this is Dr. Sauceda reminding you to list your activities and rate how you feel afterwards*"

Timing - 1) Reminders will be sent 3 and 1 day prior to the appointment date. 2) BAT activity reminders will be sent once a week during a set block of working hours, which will be determined after initial screening visit.

Two-Way Messages - All two-way messages will be initiated once a week during blocked hours of protected time (determined after screening). This will allow for messages to be sent and responded to. If two-way messages are NOT responded to during the blocked hour(s), a follow-up message will be sent to end the conversation: Example: "*Hi Miguel, please respond at your earliest convenience. I will be*

available to respond again on Thursday from 9AM and 11AM". We will minimize the risk for breaches of confidentially by never using potentially stigmatizing words in any text-messages, such as "HIV" or "depression" and acting immediately on any emergencies. All conversations will end with "*If you have an emergency, please call 911."*

During the start of all intervention sessions that are face-to-face (in person or video conference), we always discuss the acceptability of the text-message protocol. This is to discuss challenges in responding and successes, and is part of the overall evaluation of acceptability.

Content of Two-Way Messages - During designated time, the interventionist will initiate text-message conversation with participants. This is because personalizing BAT and CBT support and advice requires real-time problem-solving opportunities so participants can complete the program. For this reason, standardized messaging is not recommended as the purposes of the messaging is to continue the discussion around intervention activities that were discussed in session. Message content is derived from activities discussed in session and on file in the Microsoft Excel sheet.

Standard mood ratings sent once per week: - 1) "*Hi Miguel, this is Dr. Sauceda. How is your mood today? Reply with a number from 1 (poor) to 5 (Excellent) when convenient*." "Thank you for the response. Remember, doing a social activity like talking to a friend can help you feel better."

Problem-Solving Messages: "Hi Miguel, *do you need any help remembering the activities you planned? Reply Y for Yes, N for No." "You replied Y. You mentioned wanting to call to chat with your brother." "Can you do that today?" "How is your homework going? Can I help you in any way with the homework?" "Remember, rate how you are feeling. Let me know if you need help with the ratings." "If you have an emergency, please call 911."*

Data Collection - All study phones will store text-message communication and will be downloaded from the smart phone into a Microsoft Word document. From this document, all responses are then pasted into a secure and password protected Microsoft Excel file. The excel file lists all participant unique ID numbers, message history, and schedule preferences. The file is stored on the UCSF Box cloud storage.

6.1.2 ADMINISTRATION AND/OR DOSING

We are taking a brief behavioral intervention for depression, a text-message support intervention, and a cognitive-behavioral intervention, and sequencing how each is rolled out based on how participants respond. In a traditional approach, we would be comparing each component individually as standalone interventions compared to a control condition, and evaluating their effects. In a SMART, you start with the lowest burden/low dose intervention, and only increase as needed. This study is solely focused on feasibility and acceptability.

There are situations where multiple treatments are known to be effective, but what is unknown is whether every person benefits the same from all of them. In the depression field, we do not know how best to package what are considered efficacious interventions - 1) behavioral activation therapy, 2) cognitive-behavioral therapy, and 3) text-message support to treat depression and promote adherence to medication and clinic appointments. We will use a SMART design to evaluate if it is feasible and acceptable to sequence these behavioral interventions for depression.

STARTING POINT: Patients are recruited and then randomized to one of two active arms. The first randomization is to one of two interventions (A1 and A2). Both A1 and A2 are an already-established efficacious brief behavioral intervention, the only difference is that one will include a text-message support intervention (A1 versus A2 + Text-message support), which is the experimental factor we are testing, i.e., whether text-message support is the key factor between A1 and A2. At baseline, where participants are randomized, we will measure their depression using a standard rating scale.

FIRST OPTION: All participants will complete 4 of 8 sessions of A1 or A2, at which point we will make another depression assessment. This assessment will indicate if participants responded well to this first "assignment" (i.e., improved depression ratings) or did not respond well (i.e, no change in depression ratings or worse depression ratings). If the respond well, nothing changes and they proceed as normal through the 5-session program. If they do not respond, i.e., show no improvement or show worse ratings, we "adapt" the intervention because we have evidence that the intervention is not currently relieving depressive symptoms.

SECOND OPTION: If participants do not respond to their first assignment (e.g., no change in depression ratings or worse ratings), they are eligible to be randomized again to a second assignment (B1, B2, B3, or B4). This is why the term "sequential multiple assignment" is used because the goal is to identify how to start with A1 and "sequence" other intervention components through an "assignment" to "multiple" components (B1-B4).

Participants who did not respond to A1 or A2 (only difference is A2 has text-message support) have four options:

1. If participants in the A1 arm DO NOT improve, they can be re-randomized to either B1 to receive the text-message support component; or

2. B2 to switch to more intensive intervention, which is known as cognitive-behavioral therapy and text-message support.

3. If participants in the A2 arm DO NOT improve, they can be re-randomized to either B3 to receive one booster session of same program; or

4. B4 and switch to more intensive intervention of cognitive-behavioral therapy & text-message support.

<u>The components are</u>: 1) a brief Behavioral Activation Therapy (BAT), 2) cognitive-behavioral therapy (CBT), and a text-messaging tool (mHealth).

Patients (*N*=45) will first be randomly assigned to the first intervention component of either: A1) BAT by itself or A2) BAT & text-message support.

DICTATING CHANGE: At the first follow-up point, which is half-way through the first assignment, we will make an assessment of how they responded to the first intervention. Our goal is to measure changes in their depression ratings using a cut-off score on a clinical depression assessment tool. If their depression ratings have improved, they will maintain their initial treatment (Stay with A1 or A2), which is either: 1) BAT by itself or 2) BAT & text-message support.

If their depression ratings have not improved or get worse, we will re-randomize them to one of four additional components they have not received: B1-B4.

To summarize: BAT and CBT and mHealth are efficacious approaches to helping patients self-manage their depression. However, rather than given all patients a complex package (CBT with mHealth), we are seeking to evaluate the feasibility and acceptability of starting with a brief intervention, and then sequentially to add more intensive components only when needed.

6.2 FIDELITY

6.2.1 INTERVENTIONIST TRAINING AND TRACKING

We have two licensed psychologists and a trained cognitive-behavioral therapist on the research team who are supervising all activities. We are also using a published fidelity monitoring coding sheet to score adherence to the intervention. Interventionist will write Data-Assessment-Plan notes (DAP) for each session, which is discussed in weekly team meetings and additional trainings are discussed if fidelity to the intervention is sub-optimal.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

All randomization is done blinded. Prior to the start of the intervention, we will use the National Cancer Institutes Clinical Trial Randomization Tool stratified by English and Spanish. These randomizations will be relayed to the study coordinator who will inform the participant of their intervention starting point.

6.4 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION ADHERENCE

The acceptability outcomes are what is being evaluated to determine adherence to the intervention. Acceptability: 1) > 90% adherence to the BAT and CBT session schedule; 2) responsiveness to text messages as: a) >80% of all two-way messages replied to during the set of blocked hours; b) >90% of participants reporting direct benefit from one-way text-messages; 3) positive responses coded from post-intervention exit interview transcripts; 4) limited number of barriers to participation reported in exit interviews; and 5) responses to a brief survey (to be developed) assessing clinic staff acceptability of the intervention. Given the focus on feasibility and acceptability, the focus remains on studying whether these adherence markers can be achieved.

6.5 CONCOMITANT THERAPY

All participants will be able to receive pharmacotherapy, other psychotherapy, case management and social work services during the study, as this does not affect their eligibility and reflects the real-world circumstances of patients who may benefit from our study in the future. The implementation of the pilot SMART at ZSFG will integrate an adaptive intervention into an HIV care site, and use Spanish and English text-messages to promote adherence to the intervention. Importantly, this study will not interfere in any way with the standard of HIV primary care regularly received by patients at the ZSFG Ward 86 Clinic. Participants in a SMART are randomized to an evidence-based treatment intervention for depression, with the only differentiating factor being the use of text-messaging to support

adherence to the intervention's protocol. It is only when a patient does not respond to their assigned treatment do we investigate the next course of action in the form of a second-stage treatment, which is adapted to their particular case. Furthermore, no other services for depression, including pharmacotherapy, will be denied. For each patient, we are writing a formal letter to their HIV care provider to let them know that their patient is in this study because they reported mild to moderate depression severity and to continue to prescribe any treatment they deem appropriate. **All together, we believe that our study design, and feature of not withholding any treatment, does not place any participant at greater risk than what they would encounter with any other services available for their depression.**

6.5.1 RESCUE THERAPY

Not applicable

7 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

All participants who wish to discontinue the study will be asked for the reasons for discontinuing. This is part of the evaluation. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. This is part of the Data and Safety Plan that was submitted to the NIH and approved (This file is available upon request). Any new clinically relevant finding will be reported as an adverse event (AE).

The data to be collected at the time of study intervention discontinuation will include the following:

- The reason(s) for discontinuing the participant from the intervention, and methods for determining the need to discontinue.
- If the participant is due to complete the first assessments within 2 weeks of being discontinued from the study intervention (asking to stop with the intervention activities but willing to come in for the assessment), those assessments will be administered at the time of discontinuation; if the next scheduled assessments are more than 2 weeks from the discontinuation date, the discontinued participant will wait for the next scheduled assessment (unless they wish to completely discontinue with all study activities). Thereafter, the participant will be included in all future scheduled assessments, even though not participating in the intervention.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.
An investigator may discontinue a participant from the study for the following reasons:

- Significant study intervention non-compliance, unless varying compliance is an aspect of the study objectives

- Lost-to-follow up; unable to contact subject.
- Any event or medical condition or situation occurs such that continued collection of follow-up study data would not be in the best interest of the participant or might require an additional treatment that would confound the interpretation of the study.
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.

The reason for participant discontinuation or withdrawal from the study will be recorded. Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are discontinued from the study.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for 3 scheduled visits and study staff are unable to contact the participant after at least 3 attempts.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant, reschedule the missed visit within 1 week, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 text-messages and 2 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts will be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 ENDPOINT AND OTHER NON-SAFETY ASSESSMENTS

The focus of this study is on the feasibility of carrying out the assessment of a primary tailoring variable (PTV). A PTV is the cutoff score to decide whether a participant showed a clinically meaningful response to BAT or BAT & mHealth at a 1-month follow-up point. The preliminary cutoff score for the pilot SMART is defined as a decrease in a PHQ-9 score from the "moderate" to "mild" (or below) depression symptom severity category after 4 weeks (or after 4 of 8 sessions of BAT). The rationale for the follow-up period is to identify early who is a "responder" or "non-responder" to a 1st-stage treatment. The "responder/non-responder" decision is used to decide whether, when, and how to adapt a 1st-stage treatment. The follow-up point is the mid-way point of the brief intervention, that is, after 3 of 5 BAT sessions are complete. This cutoff score is supported by a randomized placebo-controlled trial that showed BAT to be associated with reduced depression more per week than a cognitive therapy on a self-rating scale. The same depression rating is done at the final follow-up period at the end of the final intervention session.

8.2 SAFETY ASSESSMENTS

Not applicable as this intervention does not involve any medical or pharmacological components that would warrant a physical safety assessment.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS

The definition of adverse events followed is from the U.S. Department of Health and Human Services Office for Human Research Protections. An adverse event is defined as any undesirable experience associated with the engagement with any aspect of the study activities. While the risks of any adverse events are deemed to be extremely rare, we will follow the guidance in the following sections.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS

An adverse event is serious when the patient outcome is death, life-threatening, hospitalization, disability, or other serious and important medical events.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

We will follow the Federal Guidance on this issue.

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic intervention. Severe events are usually potentially life-threatening or incapacitating.

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

All adverse events (AEs) will have their relationship to study procedures, including the intervention, assessed by an appropriately-trained interventionist and discussion in team meetings. The degree of certainty about causality will be graded using the categories below.

- **Related** – The AE is known to occur with the study procedures, there is a reasonable possibility that the study procedures caused the AE, or there is a temporal relationship between the study procedures and the event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study procedures and the AE.
- **Not Related** – There is not a reasonable possibility that the study procedures caused the event, there is no temporal relationship between the study procedures and event onset, or an alternate etiology has been established.

Our diverse team of psychologist and infectious disease and internal medicine physicians is sufficient to determine the relationship of the AE to the intervention activities.

8.3.3.3 EXPECTEDNESS

The PI along with his senior mentor have the appropriate expertise in depression and HIV care research to be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study procedures. In this behavioral intervention, we expect no serious AEs.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an AE or serious AE (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review during team meetings.

All AEs, not otherwise precluded per the protocol, will be captured following the Reporting Requirements Summary Sheet from the UCSF IRB (Attached in the IRB application). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study procedures (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study will be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical or psychiatric condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. Documentation of onset and duration of each episode will be maintained for AEs characterized as intermittent.

The interventionist will record events with start dates occurring any time after informed consent is obtained. At each study visit, the interventionist will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization. This is determined during weekly team meetings for AEs, and immediate scheduling of meetings for SAEs.

ALL SAFETY PLANS HAVE BEEN APPROVED BY THE NIMH.

8.3.5 ADVERSE EVENT REPORTING

The Reporting Requirements outlined by the UCSF Office of Ethics and Compliance will guide all reporting. The principal and co-investigators on this project will report any adverse events to the UCSF IRB within 5 working days should they be deemed related to the study AND are considered serious (defined above) or unexpected (i.e., an adverse event that exceeds the nature, severity or frequency described in the current IRB Application including the protocol and consent form)

8.3.6 SERIOUS ADVERSE EVENT REPORTING

The principal and co-investigators on this project will report to the UCSF IRB of any adverse events within 5 working days should they be deemed related to the study AND are considered serious (defined above) or unexpected (i.e., an adverse event that exceeds the nature, severity or frequency described in the current IRB Application including the protocol and consent form)

8.3.7 REPORTING EVENTS TO PARTICIPANTS

Any adverse event reported to the UCSF IRB will only be reported to the participant if it is deemed related to the study AND severe, as this is outside the scope of the risks that were discussed in the consent form, but also that the likelihood of a serious adverse event is extremely rare. Our Data and Safety Monitoring Plan approved by the NIMH also includes the ability to schedule an immediate meeting of the PI, the senior faculty mentor, and internal medical monitor.

8.3.8 EVENTS OF SPECIAL INTEREST

N/A

8.3.9 REPORTING OF PREGNANCY

N/A

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS

This protocol uses the definition of Unanticipated Problems as defined by the Office for Human Research Protections (OHRP). OHRP considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the UCSF IRB approved research protocol

and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.]

8.4.2 UNANTICIPATED PROBLEMS REPORTING

Dr. Sauceda will report unanticipated problems (UPs) to the UCSF IRB. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number.
- A detailed description of the event, incident, experience, or outcome.
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP.
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB immediately and no later than 48 hours after the discovery was made that a UP occurred.
- Any other UP will be reported to the IRB and to the DCC/study sponsor/funding agency within 5 working days of the Dr. Sauceda becoming aware of the problem .
- All UPs should be reported to appropriate institutional officials (UCSF IRB), the NIMH Program Officer, within five days of Dr. Sauceda becoming aware of the problem.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Unless the risk/benefit ratio changes or there are risks to breaches of confidentiality for the participant, no UP will be reported to them. If an UP is deemed to directly affect a participant, they will be notified that a meeting is needed to discuss how the issue will be resolved after discussion with the PI, primary mentor, and the UCSF IRB.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

There are no statistical hypotheses as this is an evaluation of feasibility and acceptability.

9.2 SAMPLE SIZE DETERMINATION

Daniel Almirall is a leading expert in SMART designs and developed a sample size estimation tool specifically for pilot SMARTs. First, we propose six treatment sequences and a minimum of four participants to receive them (called "outcome groups" in Figure 1). Second, one must estimate from the literature the percentage of participants who will not show a clinically meaningful response (i.e., "non-response rate") to a treatment they will be initially randomized to. We used data from a non-inferiority trial of cognitive therapy versus a behavioral activation therapy in general population sample. This trial used clinician-administered diagnostic tools, self-report ratings, fidelity monitoring, and had all interventions delivered by psychologists and social workers. Under these rigorous conditions, 50-60% of participants with mild depression at baseline (range based on self-report and clinician ratings) did not achieve a 50% reduction in depressive symptoms at a 4-month follow-up. Similar results were found for participants with a higher severity of depression at baseline. This estimation tool yielded a total sample size of 45 participants if we observe a non-response rate of 50-60%, a fixed probability of 80% (suggested by Almirall), a minimum of four participants per "outcome group," and a 10% attrition rate.

9.3 POPULATIONS FOR ANALYSES

The same will consist of Latinos living with HIV, no sub-analyses are planned regarding the evaluation of feasibility and acceptability.

9.4 STATISTICAL ANALYSES

9.4.1 ANALYSIS OF THE PRIMARY ENDPOINT(S)

Basic demographic tables will be generated for all depression ratings from baseline through follow-up periods, as well as general measures of central tendency for each variable (e.g., Mean, SD), measured categorical and continuously, and highlighted by measures of variability. For Feasibility, the following outcomes will be evaluated using descriptive statistics to identify: 1) the number of participants screened, eligible and enrolled; 2) at least 80% of all BAT and CBT sessions completed; and 3) 80% retention in all "outcome groups" (see attached figure in the IRB application).

9.4.2 ANALYSIS OF THE SECONDARY ENDPOINT(S)

The Microsoft Excel file will have all participant appointment attendance records and responses to schedule text-messages, which were downloaded to determine acceptability as: 1) > 90% adherence to the BAT and CBT session schedule; 2) responsiveness to text-messages as: a) >80% of all two-way messages replied to during the set of blocked hours; b) >90% of participants reporting direct benefit from one-way text messages; 3) positive responses coded from post-intervention exit interview transcripts (to be determined at future date); 4) limited number of barriers to participation reported (to be determined at a future date).

9.4.3 SAFETY ANALYSES

This section is not applicable for behavioral clinical trials.

9.4.4 BASELINE DESCRIPTIVE STATISTICS

Basic demographic tables will be generated for all characteristics at baseline, and then from baseline through follow-up periods. We will have general measures of central tendency for each variable (e.g., Mean, SD) measured categorical and continuously, and highlighted by measures of variability.

9.4.5 PLANNED INTERIM ANALYSES

There are no statistical interim analyses planned that would determine the need to stop the study given the size of this pilot study.

9.4.6 SUB-GROUP ANALYSES

There are not sub-group analyses planned as the focus of this pilot study is on Latinos living with HIV as a whole and only 10% of the clinic population is registered as female sex.

9.4.7 TABULATION OF INDIVIDUAL PARTICIPANT DATA

For descriptive purposes, depression ratings will be tabulated over the course of the intervention for each participant and in aggregate.

9.4.8 EXPLORATORY ANALYSES

There are currently not exploratory analyses that can be listed here given the pilot study was not powered to identify statistical significant relationship among the variables. Any exploratory analyses will be determined by the PI and research team.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

A copy of the informed consent processes submitted to the IRB will be available upon request.

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Participants will always be given copies of the Human Subject Bill of Rights, the HIPAA authorization form, and the consent form, unless they verbally decline to accept them.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

All consenting procedures and discussions happen in-person and in a private room or office at the study site.

The informed consent process is informed by the UCSF IRB Consent Process and Documentation guidelines and Title 45-Code of Federal Regulations regarding human subject involvement in research. The obtainment of consent will be guided by a written document and an interactive, ongoing conversation between the PI, a research assistant, or Salud and Women's Clinic staff member and a participant. All documentation and conversations are readily available in English or Spanish.

The required eight elements of consent will be sectioned paragraph-by-paragraph in the informed consent document, which will be discussed in detail with a participant. At the start of the consent process, we will let the participant know that we prefer to have the consent form read out loud while they follow along. They will have the option to read the document by themselves, but we will strongly discourage this so as to ensure all elements of consent are fully acknowledged and comprehended.

As the consent process starts, each participant must acknowledge that they understand and agree to each section before continuing on to the next section (i.e., element of consent). At each section, we will ask a participant if they understand that they have the right to refuse to participate and that there are no consequences of doing so. We will inquire about their understanding of the study procedures (including the process of notifying their provider of their participation in the study), which include the possibility of multiple treatment reassignments, participation over a three-month follow-up period, and all risks that may result from participating.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, the study site, and the NIMH. If the study is prematurely terminated or suspended, Dr. Sauceda will promptly inform study participants, IRB, and the NIMH, and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants;
- Demonstration of efficacy that would warrant stopping;
- Insufficient compliance of study staff to the protocol (ie, significant protocol violations);
- Data that are not sufficiently complete and/or evaluable;
- Determination that the primary endpoint has been met;
- Determination of futility;

The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the NIMH and UCSF IRB.

10.1.3 CONFIDENTIALITY AND PRIVACY

Given the sensitivity of the study subject matter and possible disclosure of a psychiatric or HIV diagnosis, there is the potential to face consequences. This is primarily in having their participation disclosed - a study on depression for people living with HIV. There are no direct consequences associated with not participating, participating and dropping out of the study, or completing the study. There is the possible consequence of having others (e.g., family, friends, co-workers) find out about their participation. To guard against any potential consequences, we will collect our Certificate of Confidentially (CoC) from the NIH. The CoC is available to all NIH-funded research, but can only be collected after IRB approval has been received.

The CoC information will also be specified on the consent form and described to each participant during the informed consent process. Only Dr. Sauceda, the faculty mentor, and research staff will have access to a participant's contact information and raw data. All data that will be shared with the mentoring team will be de-identified. For participants in the trial, we will create a case file that is denoted by patient ID number that is generated at the time of the enrollment. All intervention paper files will be stored in an office space and locked inside a file drawer. All consent forms and tracking forms that have identifying information will be separated from all case files. All case files will be uploaded into a password protected file and stored on a UCSF secure server. All patient text-message conversations will be stored on encrypted study mobile phones before being downloaded into a password-protected and encrypted text or EML file and stored on UCSF's secure severs.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

All data will be used for presentation and scientific conferences and peer-review publications. Aggregated data will be shared at monthly Salud Clinic meetings. No personal or identifying or singular data are ever presented.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Dr. Sauceda serves as the PI and Dr. Fernandez serves as the medical monitor (internal medicine physician). Each week, Dr. Sauceda also meets with Dr. Mallory Johnson, a licensed clinical psychologist and his senior mentor.

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10.1.6 SAFETY OVERSIGHT

All safety risks will be regularly monitored during the study. Dr. Sauceda and his senior faculty mentor (Dr. Mallory Johnson) will be in-person weekly during the study. Dr. Sauceda will also meet with Dr. Fernandez

(Internal Medical Monitor) bi-weekly during the same time period. Patient safety and data monitoring will be included as a meeting agenda item during individual meetings. The entire monitoring group will convene quarterly DSM meeting at the start of the study and up until the pilot study is completed.

10.1.7 CLINICAL MONITORING

Clinical monitoring refers to independent monitoring plans. An agreement will be made with the PI and Drs. Marquez and Gandhi (Clinic Director and Medical Director) to immediately report any detection of significant distress and breaches of confidentiality given that the study will take place at the Salud Clinic at ZSFGH. Should any breach of confidentially or adverse events occur, the PI will convene an ad hoc meeting with Drs. Johnson (faculty mentor) and Fernandez (internal medical monitor) to review options to stop the study, recommend removing the participant from the study, or change any intervention procedures to eliminate any potential risks that are occur at unacceptable levels.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

The nature and sources of data/materials collected for this study are fully described in the Protection of Human Subjects Section that is available upon request and that was approved by the NIMH. Quality assurance measures following the E6 Good Clinical Practice Guidance 1.46 will guide all research activities for this study. This will include weekly meetings with Dr. Sauceda senior faculty mentor to review each individual case and formally documented written reports of participant activity. Further, together, they will oversee the annual all-mentoring team meeting to outline progress and benchmarks of the research activities and to discuss and address any barriers and challenges to the progress of the research activities. The frequency of meetings between the PI and faculty mentor, along with co-mentors and scientific advisors, will ensure that the study progresses in accordance with the timeline outlined. Any significant delays for any study activities will be reported to the NIMH program officer.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection will be the responsibility of the research staff and Dr. Sauceda who directly supervises them. The investigator will be responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents will be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant consented/enrolled in the study.

The data systems used in this study our directly sourced from the UCSF IT Systems and includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.1.9.2 STUDY RECORDS RETENTION

Study documents will be retained for a minimum of three years after the official closeout of the study per NIH guidance.

10.1.10 PROTOCOL DEVIATIONS

This protocol defines a protocol deviation as any noncompliance with the clinical trial protocol, International Council on Harmonisation Good Clinical Practice (ICH GCP). The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions will be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- Section 4.5 Compliance with Protocol, subsections 4.5.1, 4.5.2, and 4.5.3
- Section 5.1 Quality Assurance and Quality Control, subsection 5.1.1
- Section 5.20 Noncompliance, subsections 5.20.1, and 5.20.2.

It will be the responsibility of Dr. Sauceda to use continuous vigilance to identify and report deviations within 3 working days of identification of the protocol deviation, or within 5 working days of the scheduled protocol-required activity. All deviations will be addressed in study source documents, reported to the NIMH and Program Officer Teri Senn, PhD if required. Protocol deviations will be sent to the UCSF IRB per their policies. Dr. Sauceda will be responsible for knowing and adhering to the reviewing IRB requirements.

10.1.11 PUBLICATION AND DATA SHARING POLICY

All study results and data will be compliant with the NIH Data Sharing Policy.

10.1.12 CONFLICT OF INTEREST POLICY

No persons involved with this study have any conflicts of interest.

10.2 ADDITIONAL CONSIDERATIONS

Not applicable

10.3 ABBREVIATIONS AND SPECIAL TERMS

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Council on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ITT	Intention-To-Treat
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

10.4 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale
1.0	01/20/19	Original protocol	
1.1	10/24/19	Response to initial IRB review	
1.2	10/25/19	Additional changes in response to IRB review.	
1.3	3/09/20	Limited time spent on-site for recruitment due to Covid-19	COVID-19 disruptions
1.4	06/01/2021	Change in recruitment strategies and videoconference	COVID-19 disruptions

11 REFERENCES

Almirall D, Compton SN, Gunlicks, Stoessel M, Duan N, Murphy SA. Designing a pilot sequential multiple assignment randomized trial for developing an adaptive treatment strategy. Stat Med. 2012; 31: 1887-1902.

Simoni JM, Wiebe JS, Sauceda JA, et al. A preliminary RCT of CBT-AD for adherence and depression among HIV-positive Latinos on the U.S.-Mexico Border: The Nuevo Día Study. AIDS Behav. 2013;17: 2816-2829.

STATISTICAL ANALYSIS PLAN

AIM: To test a pilot sequential multiple assignment randomized trial of a depression and mHealth treatment strategy among HIV+ Latinos for feasibility and acceptability.

Analysis of the Primary Endpoint(s)

Basic demographic tables will be generated for all depression ratings from baseline through follow-up periods, as well as general measures of central tendency for each variable (e.g., Mean, SD), measured categorical and continuously, and highlighted by measures of variability. For Feasibility, the following outcomes will be evaluated using descriptive statistics to identify: 1) the number of participants screened, eligible and enrolled; 2) at least 80% of all BAT and CBT sessions completed; and 3) 80% retention in all "outcome groups" (see attached figure in protocol).

Analysis of the Secondary Endpoint(s)

The Microsoft Excel file will have all participant appointment attendance records and responses to schedule text-messages, which were downloaded to determine acceptability as: 1) > 90% adherence to the BAT and CBT session schedule; 2) responsiveness to text-messages as: a) >80% of all two-way messages replied to during the set of blocked hours; b) >90% of participants reporting direct benefit from one-way text messages; 3) positive responses coded from post-intervention exit interview transcripts (to be determined at future date); 4) limited number of barriers to participation reported (to be determined at a future date).