Supporting Peer Interactions to Expand Access to Digital Cognitive Behavioral Therapy for Spanish-speaking Patients (SUPERA)

Study Protocol and Statistical Analysis Plan
NCT Number: *Pending*

September 18, 2022

Study Application (Version 1.3)

1.0 General Information

***Enter the full title of your study:**

SUpport from PEeRs to expand Access study

***Enter the study alias:**

SUPERA
* This field allows you to enter an abbreviated version of the Study Title to quickly identify this study.

2.0 Add departments

2.1 and Specify Research Location:

Is Primary?	Department Name
◉	**UCSF** - *133110* - M_Psych-ZSFG-Admin
○	**UCSF** - *138336* - M_MED-ZSFG-DGIM
○	**UCSF** - *133144* - M_Psych-LPPI-Rsch

3.0 List the key study personnel: (Note: external and affiliated collaborators who are not in the UCSF directory can be identified later in the Qualifications of Key Study Personnel section at the end of the form)

3.1 *Please add a Principal Investigator for the study:

Aguilera, Adrian, PhD

Select if applicable

☐ Department Chair ☐ Resident

☐ Fellow

If the Principal Investigator is a Fellow, the name of the Faculty Advisor must be supplied below.

3.2 If applicable, please select the Research Staff personnel

A) Additional Investigators

Fortuna, Lisa R MD, MPH
Other Investigator
Lyles, Courtney R PhD, PhD
Other Investigator
Ochoa-Frongia, Lisa M MD
Other Investigator
Schueller, Stephen M

Co-Principal Investigator

B) Research Support Staff

Rosales, Karina
Research Assistant

3.3 *Please add a Study Contact

Aguilera, Adrian, PhD
Rosales, Karina
Schueller, Stephen M

The Study Contact(s) will receive all important system notifications along with the Principal Investigator. (e.g. The project contact(s) are typically either the Study Coordinator or the Principal Investigator themselves).

3.4 If applicable, please add a Faculty Advisor/Mentor:

3.5 If applicable, please select the Designated Department Approval(s)

Add the name of the individual authorized to approve and sign off on this protocol from your Department (e.g. the Department Chair or Dean).

4.0 Initial Screening Questions

Updated Sept 2022 - Revised Common Rule (January 2018) Compliant / COVID-19 - v98

4.1 * PROJECT SUMMARY: (REQUIRED) Give a brief overview of this project (250 words or less). Tell us what this study is about, who is being studied, and what it aims to achieve. If you have an NIH Abstract, paste it here (Click on the orange question mark to the right for more detailed instructions):

Latinxs with Limited English Proficiency (LEP) experience longer duration of untreated mental health disorders (Gonzalez, Alegría, Prihoda, Copeland, & Zeber, 2011; Falgas, Ramos, & Herrera, et al., 2017). For depression and anxiety, Latinxs are half as likely as whites to receive quality, evidence-based care despite primary care providers recommending treatment at equivalent rates (Kim, Aguado, Chiriboga, Jang, Parmelee, & Allen, 2011; Sentell, Shumway, & Snowden, 2007). LEP Latinx patients are disproportionately on Medicaid or uninsured and therefore are more likely to receive care in public healthcare settings. Although efforts are made to integrate behavioral health into primary care in a culturally sensitive manner, there is nonetheless a severe deficiency of Spanish-speaking behavioral/mental health clinicians (Bauer, Chen, & Alegría, 2011). In addition, public healthcare systems are often under-resourced and less likely to be the site for implementation of innovations that might increase access to mental health care for their population. Multiple innovations, such as the use of technology and peer support (Kazdin, & Blase, 2011), in mental healthcare could help alleviate these problems.

Over the past decade, an increasing number of behavioral and psychological interventions have used the Internet and mobile technologies to provide efficacious treatments (Richards, & Richardson, 2012). The efficacy of such interventions has led to the recommendation that they should be frontline treatments for mental health issues including depression and anxiety ((NICE) NIfHaCE, 2006, (NICE) NIfHaCE, 2009). Despite this recommendation, few patients have access to evidence-based digital treatments, and even when available, uptake and engagement – both by providers and patients (Gilbody, Littlewood, Hewitt, et al., 2015) – is often low. As such, we need to develop and evaluate implementation strategies to support integration of digital mental

health into healthcare settings[11], especially those settings where access to evidence-based mental health care is lacking.

Digital interventions are especially relevant for low-resource settings as they are scalable and can deliver evidence-based practices with fidelity while minimizing the need for specialty mental health providers – which is critical for understaffed public delivery systems. Previous evidence has shown that human support, both by professionals as well as peers, can increase the uptake and effectiveness of digital mental health interventions. Therefore, in order to sustainably spread digital health treatment options for LEP Latinx patients treated in safety-net healthcare settings, we must test implementation strategies that include a) warm hand offs of digital mental health treatments from staff and/or providers (inreach) and registry-based outreach as well as b) the use of peers to supplement the treatment with linguistically-congruent and culturally-sensitive support and extension. Most importantly, leveraging peers for delivering digital interventions may produce solutions that are more feasible, scalable, and ultimately cost-effective than professionally-supported interventions.

In the proposed SUPERA (SUpport from PEeRs to expand Access) study, we will evaluate the implementation of an evidence-based, Spanish language, digital cognitive-behavioral therapy (dCBT) intervention (SilverCloud) in safety-net primary care clinics for LEP Latinx patients with depression and/or anxiety. We will conduct an effectiveness-implementation hybrid trial (Type 2) (Curran, Bauer, Mittman, Pyne, & Stetler, 2012) design with both provider- and patient-level randomization. At the provider-level we will compare outreach (using our clinic patient registry) with inreach (traditional provider referral), at the patient-level we will compare two modes of delivery of the dCBT platform – peer-supported and unsupported. The SUPERA study will involve implementation into the San Francisco Health Network at the Zuckerberg San Francisco General Hospital serving 21,076 patients. Our previous work has included providing digital and mental health treatments to this same population.

4.2 * HUD DEVICE: (REQUIRED) Does this application involve a Humanitarian Use Device (HUD):

- (•) No
- ( ) Yes, and it includes a research component
- ( ) Yes, and it involves clinical care ONLY

4.3 * TYPE OF RESEARCH: (REQUIRED) Select the option that best fits your project (Click the orange question mark to the right for definitions and guidance):

- ( ) Biomedical research (including medical records review, biospecimen collection and/or use, other healthcare or health outcomes related activities, research database, biospecimen bank, or recruitment registry)
- (•) Social, behavioral, educational, and/or public policy research
- ( ) Hybrid - includes aspects of BOTH types of research (check this option if your research is mainly social/behavioral but also involves specimen collection or blood draws to look at biological measures)

4.4 * SUBJECT CONTACT: (REQUIRED) Does this study involve ANY contact or interactions with participants:

- (•) Yes (including phone, email or web contact)
- ( ) No (limited to medical records review, biological specimen analysis, and/or data analysis)

4.5 * RISK LEVEL: (REQUIRED) What is your estimation of the risk level, including all screening procedures and study activities:

- (•) Minimal risk
- ( ) Greater than minimal risk

4.6 * REVIEW LEVEL: (REQUIRED) Requested review level (Click on the orange question mark to the right for definitions and guidance):

◉ Full Committee
○ Expedited
○ Exempt

Generally, only *Greater than Minimal Risk* studies require *Full Committee Review*. We suggest you check *Expedited Review* instead or change the risk level, if you checked the wrong box.

4.9 * DATA/SPECIMEN ANALYSIS ONLY: (REQUIRED) Does this study ONLY involve records review and /or biospecimen analysis (do not check 'Yes' if this is a registry, research or recruitment database, or biospecimen repository):

○ Yes ◉ No

4.10 * CLINICAL TRIAL: (REQUIRED)
Is this a clinical trial:

According to The World Health Organization (WHO) and the International Committee of Medical Journal Editors (ICMJE) a clinical trial is:

- Any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes.

ICMJE requires registration of a clinical trial in a public database (such as ClinicalTrials.gov) prior to enrollment, for eventual publication of results in member biomedical journals.
Guidance: Public Law 110-85 requires that all investigators who perform an *applicable clinical trial* must ensure that the trial is registered on a government web site called **ClinicalTrials.gov**.

The FDA requires registration for 'applicable clinical trials,' defined as follows:

- For any trials of drugs and biologics: controlled clinical investigations, other than Phase 1 investigations, of a product subject to FDA regulation.
- For trials of biomedical devices: controlled trials with health outcomes of devices subject to FDA regulation, other than small feasibility studies, and pediatric post-market surveillance.

For additional information on the **ClinicalTrials.gov** registration process at UCSF and the definition of a clinical trial for purposes of registration, visit the **ClinicalTrials.gov section of the UCSF Clinical Research Resource HUB**.

◉ Yes ○ No

Clinical Trial Registration - 'NCT' number for this trial:

Pending

4.11 * CLINICAL TRIAL PHASE: (REQUIRED) Check the applicable phase(s):

- [ ] Phase 0
- [ ] Phase 1
- [ ] Phase 1/2
- [ ] Phase 2
- [x] Phase 2/3
- [ ] Phase 3
- [ ] Phase 4
- [ ] Not Applicable

4.12 * INVESTIGATOR-INITIATED: (REQUIRED) Is this an investigator-initiated study:

(•) Yes ( ) No

The UCSF IRB recommends use of the Virtual Regulatory Binder to manage your study.

4.13 * CORONAVIRUS RESEARCH: (REQUIRED) Does this study involve research on coronaviruses (COVID-19, SARS, MERS or other):

( ) Yes (•) No

4.15 * CANCER: (REQUIRED) Does this study involve cancer (e.g., the study involves patients with cancer or at risk for cancer, including behavioral research, epidemiological research, public policy research, specimen analysis, and chart reviews):

( ) Yes (•) No

4.16 * RADIATION EXPOSURE: (REQUIRED) Does your protocol involve any radiation exposure to patients /subjects EITHER from standard care OR for research purposes (e.g., x-rays, CT-scans, DEXA, CT-guided biopsy, radiation therapy, or nuclear medicine including PET, MUGA or bone scans):

( ) Yes (•) No

4.17 * HIV SCREENING: (REQUIRED)Does this study involve screening for HIV infection:

You should answer 'Yes' if the protocol includes HIV testing even if it's just for screening to determine eligibility.

( ) Yes (•) No

4.18 * SCIENTIFIC REVIEW: (REQUIRED) If this study has undergone scientific or scholarly review, please indicate which entity performed the review (check all that apply):

- [x] Funding agency, cooperative group, study section or other peer-review process
- [ ] Cancer Center Protocol Review Committee (PRC) (Full approval is required prior to final IRB approval for cancer-related protocols.)
- [ ] CTSI Clinical Research Services (CRS) Advisory Committee
- [ ] Departmental scientific review
- [ ] CTSI Consultation Services
- [ ] Other:
- [ ] Has not undergone scientific/peer review

* Specify entity that provided review: **(REQUIRED)**

National Institute of Mental Health

4.19 * STEM CELLS: (REQUIRED)Does this study involve human stem cells (including iPS cells and adult stem cells), gametes or embryos:

- (•) No
- ( ) Yes, and requires IRB and GESCR review
- ( ) Yes, and requires GESCR review, but NOT IRB review

4.20 * FINANCIAL INTERESTS: (REQUIRED) Do you or any other responsible personnel (or the spouse, registered domestic partner and/or dependent children thereof) have financial interests related to this study:

( ) Yes (•) No

5.0 Funding

5.1 * FEDERAL FUNDING: (REQUIRED) Is this study currently supported in whole or in part by Federal funding, *even by a subcontract*, OR has it received ANY Federal funding in the past:

(•) Yes ( ) No

* UCSF requires the PI to certify that the research activities described in their IRB application are consistent with those described in the fiscal and materials sources of support listed in the grant application(s). Check the relevant box below: **(REQUIRED)**

- (•) The research activities described in this application are wholly consistent with those described in the grant application(s)
- ( ) The research activities described in this application differ from those described in the grant application (or, if there are multiple federal grants, the research activities described in this application differ from those described in one or more of the grant applications). Explain the discrepancies in the designated box within the funding details area below.
- ( ) This study is partially or fully supported with federal funds but there's no grant.

5.2 * DoD INVOLVEMENT: Is this project linked in any way to the Department of Defense (DoD): (REQUIRED)

( ) Yes (•) No

5.3 SPONSORS: Identify all sponsors and provide the funding details. If funding comes from a Subcontract, please list only the Prime Sponsor:

External Sponsors:

View Details	Sponsor Name	Sponsor Type	Awardee Institution:	Contract Type:	Project Number	UCSF RAS System Award Number ("A" + 6 digits)

⊟	NIH Natl Institute of Mental Health	01	Other (No funding comes through UCSF C&G unit)			

Sponsor Name:	NIH Natl Institute of Mental Health
Sponsor Type:	01
Sponsor Role:	Funding
CFDA Number:	
Grant/Contract Number:	1R01MH126664
Awardee Institution::	Other (No funding comes through UCSF C&G unit)
Is Institution the Primary Grant Holder:	No
if No, then who is the Primary Grantee?	University of California, Irvine
Contract Type:	
Project Number:	
UCSF RAS System Award Number ("A" + 6 digits):	
Grant Number for Studies Not Funded thru UCSF:	
Grant Title:	
PI Name: (If PI is not the same as identified on the study.)	Stephen Schueller, PhD
Explain Any Significant Discrepancy:	

Other Funding Sources and Unfunded Research - Gift, Program, Departmental or other Internal Funding (check all that apply):

- ☐ Funded by gift (specify source below)
- ☐ Funded by UCSF or UC-wide program (specify source below)
- ☐ Specific departmental funding (specify source below)
- ☐ Unfunded (miscellaneous departmental funding)
- ☐ Unfunded student project

6.0 Sites, Programs, Resources, and External IRB Review

6.1 * UCSF AND AFFILIATED SITES (check all that apply): (REQUIRED)

- ☐ UCSF Benioff Children's Hospital Oakland (BCH OAK)
- ☐ UCSF Cancer Center Berkeley
- ☐ UCSF Cancer Center San Mateo
- ☐ UCSF China Basin clinics and facilities
- ☐ UCSF Helen Diller Family Comprehensive Cancer Center
- ☐ UCSF Langley Porter Psychiatric Institute (LPPI)
- ☐ UCSF Medical Center at Mission Bay (Benioff Children's Hospital, the Betty Irene Moore Women's Hospital, Bakar Cancer Hospital, or outpatient clinics)
- ☐ UCSF Mount Zion
- ☐ UCSF Parnassus (Moffitt-Long hospital, dental clinics or other outpatient clinics)
- ☐ UCSF Other Sites (including Laurel Heights and all the other sites outside the main hospitals

and clinics)

- [ ] UCSF Fresno
- [ ] Gladstone Institutes
- [ ] Institute on Aging (IOA)
- [ ] Jewish Home
- [ ] SF Dept of Public Health (DPH)
- [ ] San Francisco VA Health Care System (SFVAHCS) – including Community-Based Outpatient Clinics (CBOCs)
- [ ] Vitalant (formerly Blood Centers of the Pacific and Blood Systems Research Institute)
- [x] Zuckerberg San Francisco General (ZSFG)

Research involving SFDPH/ZSFG: A UCSF Research at SFDPH Protocol Application is required for all research. Review this link for more information and contact information for SFDPH/ZSFG questions. SFDPH sites and clinics have special requirements that you must be familiar with. The UCSF IRB will only review SFDPH IRB Applications with designated SFDPH PIs.

6.2 * LOCATIONS: At what locations will study visits and activities occur: (REQUIRED)

The Richard Fine People's Clinic (RFPC) and the Family Health Center (FHC) at ZSFGH will serve as the study sites.

Enrollment procedures will take place at ZSFG.

6.3 OFF-SITE PROCEDURES: Will any study procedures or tests be conducted off-site by non-UCSF personnel:

- (•) Yes
- ( ) No

Please identify which procedures may be done off-site:

Peers supporters which are affiliated with community organizations will conduct weekly check-ins with study participants and study staff. Supporters will be supervised by study staff.

6.4 RESEARCH PROGRAMS: Check any UCSF research programs this study is associated with:

- [ ] Cancer Center
- [ ] Center for AIDS Prevention Sciences (CAPS)
- [ ] Global Health Sciences
- [ ] Immune Tolerance Network (ITN)
- [ ] Neurosciences Clinical Research Unit (NCRU)
- [ ] Osher Center
- [ ] Positive Health Program
- [ ] Weill Institute for Neurosciences Translational Research Unit (WIN TRU)

6.5 * CTSI CRS SERVICES: (REQUIRED)Will this study be carried out at one of the UCSF Clinical Research Services (CRS) Units or utilize CRS Service:

- ( ) Yes
- (•) No

6.6 * MULTI-CENTER TRIAL: (REQUIRED) Is this a multi-center or multi-site research trial:

By **'multi-center trial**' we mean a study where the protocol is developed by an lead investigator, an industry sponsor, consortium, a disease-group, etc.,and multiple sites across the nation or in different countries participate in the trial. The local sites do not have any control over the design of the protocol.

○ Yes ◉ No

6.8 OTHER SITE TYPES: Check all the other types of sites not affiliated with UCSF with which you are cooperating or collaborating on this project:

Do NOT check any boxes below if this is a multi-center clinical trial, UCSF is just one of the sites, and neither UCSF nor one of its faculty-linked affiliates (SF VAHCS, Gladstone, ZSFG) are the coordinating center.

- ☑ Other UC Campus
- ☐ Other institution
- ☐ Other community-based site
- ☐ Foreign Country
- ☐ Sovereign Native American nation (e.g. Navajo Nation, Oglala Sioux Tribe, Havasupai, etc.)

6.9 OTHER UC COLLABORATORS: Check any other UC campuses with which you are collaborating on this research study:

- ☑ UC Berkeley
- ☐ UC Davis
- ☐ Lawrence Berkeley National Laboratory (LBNL)
- ☑ UC Irvine
- ☐ UC Los Angeles
- ☐ UC Merced
- ☐ UC Riverside
- ☐ UC San Diego
- ☐ UC Santa Barbara
- ☐ UC Santa Cruz

6.10 UC RELIANCES: Are any of the above UC campuses requesting to rely on UCSF's IRB (check all that apply)?

- ☑ Yes
- ☐ No

6.15 * RELYING ON AN EXTERNAL IRB: (REQUIRED) Does this application include a request to rely on an external IRB (a central IRB (other than the NCI CIRB) or an external IRB (other UC campus, commercial, or institutional):

○ Yes ◉ No

6.16 * RELIANCE AGREEMENT TYPE: (REQUIRED) Under what Reliance Agreement is UCSF being requested to rely:

- [x] UC MOU
- [ ] SMART IRB
- [ ] Established Consortium Agreement, if applicable
- [ ] Private IRB Master Service Agreement
- [ ] Other (specify below)
- [ ] Unknown

6.18 * UC RELIANCE REGISTRY NUMBER: What is the UC IRB Reliance Registry Number: (REQUIRED)

Study #3995: SUpport from PEeRs to expand Access (SUPERA)

7.0 Research Plan and Procedures

7.1 * HYPOTHESIS: Describe the hypothesis or what the study hopes to prove: (REQUIRED)

Hypothesis 1: We predict peer-supported dCBT will result in greater improvement in mental health symptoms (co-primary outcomes, as measured by PHQ-9 and GAD-7) and functioning (secondary outcomes, as measured by PROMIS social health) and higher patient engagement (secondary outcome and mediator, as measured by time on platform) compared to unsupported dCBT.

Hypothesis 2: We predict an outreach (registry based direct-to-consumer) strategy will result in more patients referred, more patients initiating, and lower relative cost compared to inreach (provider referral).

7.2 * AIMS: List the specific aims: (REQUIRED)

Aim 1: Evaluate patient-level randomization in the SUPERA study on effectiveness of dCBT modalities. Patients who initiate dCBT will be randomized to a two-armed trial comparing peer-supported vs. unsupported dCBT (SilverCloud).

Aim 2: Evaluate provider-level randomization in the SUPERA study on implementation strategies. We will use block randomization to assign blocks of providers to a two-armed trial comparing outreach vs. inreach. Implementation evaluation will follow the RE-AIM model. The primary outcome will be reach as defined by the proportion of eligible patients referred and initiating dCBT comparing outreach vs inreach strategies.

Aim 3: Evaluate putative mechanisms of change for the intervention and implementation strategies. We will conduct a mixed-methods evaluation consisting of surveys, interviews, and focus groups. Aim 3a): We will include patients and peers to assess attitudes towards the intervention, support component, cultural relevance as well as relationship factors and CBT skills use, knowledge, and fit. Aim 3b): We will include clinic leadership and providers to assess climate, clinic readiness, and attitudes towards the intervention, including potential for sustainability. This will provide rich contextual and process information for the implementation evaluation.

7.3 * DESIGN: Briefly describe the study design (e.g., observational, interventional, randomized, placebo-controlled, blinded, cross-over, cross-sectional, longitudinal, pharmacokinetic, etc.): (REQUIRED)

We will implement dCBT in the SFHN focusing on the two clinics that cover most of the Latinx patients within the SFHN at ZSFG. Providers will be block randomized by clinic to the implementation conditions (i.e., outreach vs. inreach) while patients who enroll to receive dCBT will be randomized to two delivery modes (peer-supported vs. unsupported). Our target is to enroll 390 LEP Latinx patients.

7.4 * BACKGROUND AND SIGNIFICANCE: Briefly provide the background and significance of this study (e.

g. why is this study needed) (space limit: one half page): (REQUIRED)

Depression and Anxiety Treatment Disparities among LEP Latinxs. Latinxs experience increased rates, severity, or persistence of mood and anxiety disorders compared to their non-Latinx white counterparts (Vilsaint, NeMoyer, & Fillbrunn, et al., 2019; Escovar, Craske, & Roy-Byrne, et al., 2018). In addition Latinxs with LEP who have depression and/or anxiety disorders take longer to receive treatment and when they do, they typically receive lower quality of care (Bauer, Chen, & Alegría, 2010; Wells, Klap, Koike, & Sherbourne, 2001). In general, two-thirds of people with common mental health issues (e.g., depression and anxiety) want psychological help (Brody, Khaliq, & Thompson, 1997; Dwight-Johnson, Sherbourne, Liao D, & Wells, 2000; Bedi, Chilvers, & Churchill, et al., 2000; Priest, Vize, Roberts, Roberts, & Tylee, 1996; Churchill R, Khaira M, Gretton V, et al., 2000) and ethnic minorities are even more likely to prefer psychosocial services to antidepressant medication (Givens, Houston, Van Voorhees, Ford, & Cooper, 2007). Latinxs show even higher rates of under-utilization of mental health services than whites (31% versus 48% of non-Latinx whites) for various reasons including time constraints, transportation problems, availability of services, stigma, and cost (Interian, Ang, Gara, Rodriguez, & Vega, 2011; Quality AfHRa. 2016). Additionally, even when Latinx receive mental health services, engagement is lower. They are more likely to drop out and receive fewer sessions (Chavira, Golinelli, & Sherbourne, et al., 2014), which negatively effects clinical outcomes (Forde, Frame, & Hanlon, et al., 2005; Hansen, & Lambert, 2003; Nieuwsma, Trivedi, McDuffie, Kronish, Benjamin, & Williams, 2011). Reasons for lower engagement in Latinxs include a lack of providers and unsatisfactory interactions between patients and providers due in part to cultural and linguistic differences (EL E, 2019).

Primary care is the de facto treatment setting for the treatment of common mental health issues like depression and anxiety (Frank, Huskamp, & Pincus, 2003). Many Latinxs prefer to remain in primary care for treatment rather than being referred to specialty mental health providers, they also prefer psychosocial options, especially those that improve accessibility such as short-term treatments (e.g., single sessions) or tele-therapy (Dwight-Johnson, Lagomasino, & Hay J, et al., 2010). However, patients treated in primary care are nearly 4 times as likely to receive antidepressant medication than psychotherapy (87.0% vs. 23.2%)(Olfson, Blanco, & Marcus, 2016). Thus, treatment models that increase access to psychosocial interventions in primary care might be particularly well-suited to reduce disparities in access and benefits in mental health services for Latinx populations (Dwight-Johnson, Lagomasino, & Hay J, et al., 2010).

Spanish-speaking workforce shortages. However, there is an extreme shortage of Spanish-speaking mental health providers that limits the ability to disseminate psychosocial interventions. In California, where our proposed work will take place, 40% of the overall populations is Latinx, whereas only 4% of Psychiatrists, 8% of Psychologists, and 24% of Social workers are Latinx (Auntré, Karen, Luona, & Peggy, 2016). Therefore, it is not feasible for all who need services in Spanish, to receive them. Even when an interpreter is used, Spanish-speakers report feeling less comfortable sharing personal information with an English-speaking therapist (Nguyen, 2014).

Implementation strategies are needed to improve uptake among LEP Latinxs. Warm handoffs (i.e., inreach) are commonly implemented to increase engagement in integrated behavioral health; however, this approach is less effective among LEP Latinxs (Horevitz, Organista, & Arean, 2015). Lack of culturally- and linguistically-concordant providers could be one reason for lower effectiveness. Consolidating referrals using a registry-based approach (i.e., outreach) could be a more efficient use of Spanish-speaking staff. The available research indicates that structural and cultural barriers to care can be addressed through improved outreach strategies, which include registry-based case finding and reaching out to and motivating patients to seek early and/or sustained care before they arrive in the clinical setting (Yabroff, O'Malley, Mangan, & Mandelblatt, 2001; Fuzzell, Perkins, Christy, Lake, & Vadaparampil, 2020). In-reach (e.g., clinic-based warm handoffs) and outreach strategies (e.g., registry-based identification) have been successfully applied to cancer screening (Fuzzell, Perkins, Christy, Lake, & Vadaparampil, 2020) and prenatal care engagement in underserved populations (Guendelman, & Witt, 1991). Inreach and outreach each provide benefits and limitations, and it is important to understand which works best for engaging LEP Latinx in care. Outreach might be especially relevant for interventions that facilitate better direct-to-consumer strategies (Becker, 2015), such as digital interventions. Given open questions about effectiveness of inreach and outreach, our study will compare these two strategies to promote adoption in low-resourced clinic settings.

Efficacy of Digital Cognitive-Behavioral Therapy (dCBT). A growing number of trials suggest that digital interventions, especially when coupled with human support, can produce reductions in symptoms of anxiety and depression that are similar to those seen for psychotherapy and pharmacotherapy. A recent meta-analysis of dCBT summarizing 39 studies and 9,571 patients found that both supported and unsupported dCBT showed superiority to treatment as usual and waitlist controls, and that supported dCBT was superior to unsupported dcBT (Karyotaki, Efthimiou, Miguel, et al., 2021). Even in clinic settings, a recent randomized trial comparing a

coached dCBT platform to treatment-as-usual for anxiety and depression in internal medicine clinics found greater reductions in symptoms of anxiety and depression and higher rates of recovery among patients who received dCBT (Graham, Greene, & Kwasny, et al., 2020). The strength and consistency of support for dCBT has led to recommendations that dCBT should be a frontline treatment for anxiety and depression ((NICE) NIfHaCE, 2006; (NICE) NIfHaCE, 2009). Examples of successful deployments of dCBT to increase access to effective care can be found globally including in Australia (Titov, Dear, Staples, et al, 2017; Titov, Dear, Nielssen, et al, 2018) and the UK (Duffy, Enrique, Connell, Connolly, Richards, 2019). 96% of Spanish-speaking patients in our clinic settings own smartphones, making dCBT a viable delivery mechanism with potential for sustainable delivery.

Although many dCBT platforms exist, few of the widely available platforms have undergone rigorous empirical evaluations especially in clinical settings. Most evaluations have used a small set of users (Moberg, Niles, & Beermann, 2019; Dryman, McTeague, Olino, & Heimberg, 2017) or taken place in controlled settings (Parks, Williams, Tugade, et al., 2018). One notable exception is SilverCloud. Initial research on the impact and user experience of the SilverCloud platform was published in 2012 (Doherty, Coyle, D., Sharry, 2012). Since then, SilverCloud has been used by more than 500,000 users and been involved in multiple trials including efficacy trials (Richards, Timulak, O'Brien, et al. 2015),pragmatic trials (Duffy, Enrique, Connell, Connolly, & Richards, 2019; Richards, Enrique, & Eilert N, et al., 2020), and evaluations of adaptations of SilverCloud including cultural and linguistic adaptations in Mexico and Colombia in Spanish (Salamanca-Sanabria, Richards, Timulak, 2019; Salamanca-Sanabria, Richards, & Timulak, et al., 2020). SilverCloud is currently being evaluated for college students in Colombia and Mexico (R01 MH120648, PI: Benjet), and we are currently involved in a PCORI-funded evaluation of guided and unguided SilverCloud among Medicaid recipients in West Virginia (PCS-2017C3-9252, PI: Bossarte). The choice of a dCBT intervention with strong evidence of efficacy is consistent with NOT-MH-18-031 on NIMH high-priority areas for research on digital health to use existing commercial digital health applications in NIMH-funded research.

Although human support is recognized as an essential component of the most effective dCBT programs, including support significantly reduces the scalability of dCBT. This is especially true for traditionally underserved populations, like LEP Latinx, as in most instances human support is offered by specialty mental health providers and significant workforce shortages exist. Despite this reliance on specialty providers as supporters for dCBT, evidence suggests that with some training non-specialty personnel (e.g., technicians, research assistants) can achieve results similar to professionals (Titov, Andrews, Davies, McIntyre, Robinson, Solley, 2010). Given the dearth of Spanish-speaking providers, reducing the reliance on professionals might increase the ability to implement and scale such programs, especially in low-resource settings, and ultimately increase their impact.

Peer-Supported Programs. One evidence-based solution to overcome the limitations (e.g., language, scalability, cost) associated with professional support is utilizing peers and lay supporters. Peer support might be especially relevant for Latinx patients who report appreciating culturally-appropriate care. Such care often integrates factors such as "simpatia" or support received by interacting with people who understand and have experience with their sociocultural context (Aguilera, Garza, & Muñoz, 2010). Furthermore, the work of peers, including community health workers or promotoras in the Latinx community, has been particularly helpful for improving access to mental health care in underserved and under-resourced settings (Barnett, Gonzalez, Miranda, Chavira, & Lau, 2018; Hoeft, Fortney, Patel, & Unützer, 2018). Although some work has found positive responses among stakeholders when trained promotoras are used to address social determinants of depression in primary care, improvements in depression symptom severity were not found (Waitzkih, Getrich, & Heying, et al., 2011). More recent studies have found that promotoras may be helpful in intervention task sharing, improving patient care management and engagement in evidence-based behavioral health care, and by understanding socio-cultural context in overcoming stigma and for supporting therapeutic alliance, engagement and retention in care (Hoeft, Fortney, Patel, & Unützer, 2018). Thus, including peers to support mental health service delivery via a dCBT platform combines the evidence-based clinical content with increased alliance, engagement, and retention that peers provide.

In California, where this work will be conducted, recent legislation (SB 803) supports the certification and payment for peer support specialists in mental health service delivery under Medi-Cal. This bill aligns with programs in most other states to certify and reimburse for peer support specialists. As such, leveraging peers as supporters in dCBT platforms may be a scalable and sustainable strategy if demonstrated effective.

Summary of Significance. Clear treatment gaps exist in access to mental health services, especially among LEP Latinx patients. With the increase in remote and digital services related to COVID, the potential for digital treatments is beginning to be realized, but the gaps integrating such technologies into practice settings, especially to meet the needs of traditionally underserved populations are clear. We need implementation strategies tailored for delivery of digital care and

service delivery models that can overcome workforce limitations such that inequities are not merely repeated in a digital medium. dCBT is a best-in-class, evidence-based, digital intervention and SilverCloud is one of the most researched commercial examples of dCBT. However, consistent with this PA, there is a need to determine the effectiveness of strategies to deliver evidence-based treatments in low-resource and non-specialty settings where evidence-based practices are not currently being delivered. This study focuses on these questions in digital care delivery and implementation.

7.5 PRELIMINARY STUDIES: Briefly summarize any preliminary studies relevant to your proposed research (space limit: one half page):

Previous work in Digital Interventions in Latinx Primary Care Mental Health. Our team has conducted extensive work implementing culturally-relevant CBT and digital interventions in primary care settings in the public sector among Spanish-speaking populations (Aguilera, Garza, & Muñoz, 2010; Aguilera, & Muñoz, 2011; Aguilera, & Berridge, 2014; Aguilera, Bruehlman-Senecal, Liu, & Bravin, 2018; Garcia, Ochoa-Frongia, Moise, Aguilera, & Fernandez, 2018; Aguilera, Ramos, Sistiva, Wang, & Alegria, 2018). We have shown that engagement in depression treatment is a challenge for patients in public sector primary care clinics (Aguilera, Bruehlman-Senecal, Liu, & Bravin, 2018).Dr. Aguilera developed and tested an automated text messaging adjunct to the BRIGHT group depression treatment among Spanish speakers with depression resulting in increased engagement (Aguilera, & Muñoz, 2011; Aguilera, & Berridge, 2014; Aguilera, Bruehlman-Senecal, Demasi, Avila, 2017).This foundational work showed that LEP Latinx can and will engage with digital interventions.

Drs. Aguilera and Lyles are currently conducting a study using a mobile app-based intervention to increase physical activity among patients with depression and diabetes. They have demonstrated how technology-based interventions can be designed for underserved populations (Aguilera, Bruehlman-Senecal, Demasi, & Avila, 2017; Avila-Garcia, Hernandez-Ramos, & Nouri, et al., 2019; Nouri, Avila-Garcia, Cemballi, Sarkar, Aguilera, Lyles, 2019) and have recently gained experience conducting remote recruitment for research studies due to the COVID-19 pandemic.

Dr. Fortuna has extensive experience conducting trials of digital programs in health care settings. Her work has highlighted the importance making the burden on providers low, while integrating training in technology use in supported digital interventions. We are including all of these aspects into our trial, including our peer training and support protocol. Last, her interviews showed that during COVID-19 pandemic participants have had an opportunity to use and become more comfortable with telepsychiatry and virtual care.

Previous work in Supported dCBT. Dr. Schueller has extensive work in the development, evaluation, and implementation of dCBT, including for LEP Latinx patients. He was a co-I on two recently completed trials of dCBT for depression (R01 MH100482, R01 MH095753), and is a co-I on a recently funded trial of dCBT for depression among cancer patients with a specific focus on Latinx patients (R37 CA255875). The two completed randomized trials found that dCBT was effective at reducing depression and anxiety (Mohr, Lattie, Tomasino, et al., 2019; Mohr, Schueller, Tomasino, et al., 2019) and also that stepped care using dCBT was noninferior to telephone CBT, demonstrating comparability with other forms of CBT delivery, and that it was significantly less costly, mostly due to reduced therapist time (Mohr, Lattie, Tomasino, et al., 2019), demonstrating promising potential for sustainability.Both of these studies involved supported dCBT and the coaching support manual (Tomasino, Noth, Bardsley, Lattie, Mohr, 2016) from these studies will be used for this proposed SUPERA study (although translated into Spanish). The support manual is based on the supportive accountability model (Parks, Williams, & Tugade, et al., 2018) and the efficiency model ((NICE) NIfHaCE, 2006) (developed by PI Schueller). The efficiency model forms our conceptual model for evaluating the patient-level effectiveness (Aim 1; clinical outcomes of depression and anxiety; adherence is patient adoption) and understanding the putative mechanisms of support (Aim 3a). Specifically, we will assess relational factors including bond, accountability, and legitimacy and technique factors including skill fit (i.e., cultural relevance and effectiveness), skill use, and knowledge (CBT skill knowledge). This work shows our capacity to conduct clinical trials of dCBT, to train and supervise supporters, and provides the conceptual model that elucidates our change mechanisms hypothesized to account for intervention effects.

Dr. Schueller leads the Implementation Evaluation Core for the Help@Hand Evaluation Team. Help@Hand is a multi-year innovation project representing a collaboration between 14 California city and county behavioral health departments to explore the use of technology to improve the reach and impact of mental health services. As part of this project, Dr. Schueller has designed and conducted multi-level, mixed-methods evaluations including interviews, surveys, and workflows observations. Within this project a recent pilot explored the use of dCBT to enhance wellbeing and social connectedness among isolated older adults. This pilot consisted of 30 isolated

older adults, half of which were monolingual Spanish speakers. The English speakers were supported by nurse interns and the Spanish speakers were supported by promotoras. A majority of these participants found dCBT useful (74%), easy to use (65%), and would recommend it to someone else (78%). Furthermore, they found dCBT to be a culturally-appropriate treatment (78%). Supporters found dCBT to be usable (73%), safe (100%), and useful (80%) for their clients, and appropriate for their work (67%). However, interviews identified opportunities for improvement including additional orientation to the dCBT platform, guidance to fit its use into their busy lives, and further opportunities for enhanced cultural tailoring. These issues will be addressed using our peer support protocol.

7.6 * TREATMENT PROTOCOL: Is this a treatment study, i.e. does this study intend to provide treatment to individuals with a medical or psychological condition: (REQUIRED)

(•) Yes ( ) No

7.7 * BILLABLE PROCEDURES: Does this study involve any procedures, lab tests or imaging studies that have a CPT code and could be billable to patients, their insurance, Medi-Cal, Medicare, or any other entity (answer 'Yes' even if the study is going to pay for all the procedures): (REQUIRED)

( ) Yes (•) No

If you are not sure if your study involves billable procedures, send an email to the UCSF Office of Clinical Research (OCR) for help answering this question.

7.8 * COMMON RESEARCH ACTIVITIES: Types of research activities that will be carried out. Check all that apply and describe in more detail in the 'Procedures / Methods' section: (REQUIRED)

- [x] Interviews, questionnaires, surveys
- [ ] Educational or cognitive tests
- [ ] Focus groups
- [ ] Social media-based research activities
- [ ] Observation
- [ ] Fitness tests or other exertion activities
- [x] Use of mobile health apps or other apps
- [ ] Collection of data from wearable tech such as Fitbit, Apple Watch, Garmin, motion actigraphs, etc.)
- [ ] Non-invasive imaging or testing (MRI, EEG, pulse oximetry, etc.)
- [ ] Imaging procedures or treatment procedures that involve radiation (x-rays, CT scans, CT-guided biopsies, DEXA scans, MUGA or PET scan)
- [ ] Administration of contrast agent
- [x] Randomization to one intervention versus another
- [ ] Use of placebo
- [ ] Biopsy conducted solely for research purposes
- [ ] Sham surgical procedure
- [ ] None of the above

7.9 * PROCEDURES / METHODS: (REQUIRED)

Describe the research methods and study activities taking place at each site (e.g. what will participants be asked to do and what will members of the study team do?). If there will be multiple participant groups or study sites, explain what will happen with each group or study sites.

If some of the activities would occur even if the person were not in the study, as in the case of treatment or tests performed for diagnostic purposes, **clearly differentiate between those activities that will be done solely for research purposes and those that are happening as part of routine care.**

Please call our office at 415-476-1814 and ask to speak to someone on the Expedited Review team if you need help differentiating between what parts are research and what parts aren't.

Our dCBT intervention will be announced to PCPs and behavioral health clinicians in participating clinics along with education about inclusion and exclusion criteria. Our first level of randomization will be at the provider level. Patients will be recruited in two ways: 1) For providers who are randomly assigned to "outreach" our team will use the registry for recruitment. A study team member will contact PCPs with a list of their patients eligible for inclusion to seek their approval to recruit patients, send a letter and will then contact eligible patients to offer the intervention. Additionally, patients identified as eligible through the registry will receive a flag in the EHR so that the provider can introduce the study to them, and 2) For providers who are randomly assigned to the "inreach" condition any patient of the providers in this condition may be referred for dCBT by their PCP or corresponding behavioral health clinician and our team will confirm eligibility.

Outreach. Outreach will be a direct-to-patient implementation strategy that will leverage the patient registry at ZSFG. This registry is based on patient- and provider-reported data and demographics in the Epic electronic health record (EHR). Registry reports can be pulled based on validated population health management tools in Epic, specifically the Healthy Planet tool. These reports include patient demographics and primary care provider problem list diagnoses and visit diagnoses and any structured assessment data including PHQ-9 (Patient Health Questionnaire-9) and/or GAD-7 (Generalized Anxiety Disorder 7). Thus, preference for Spanish, a diagnosis of depression or anxiety on the problem list or visit summary or PHQ-9 and/or GAD-7 scores will all be available on these reports. In the outreach strategy, potentially eligible patients will be identified and contacted. First mode of contact will be through a letter presenting the study, sent on behalf of the research team by the patient's clinic, providing information about how to opt out of further contact, prior to phone contact by the research team. This will be followed by a scripted phone call providing an introduction to SilverCloud. These phone calls will be followed by a video call orientation or a letter from the clinic, culturally-tailored introduction to SilverCloud, and a referral to receive login instructions. SilverCloud's integration with Epic EHR will make referral and data collection streamlined. Research team will attempt to contact eligible participants a total of 3 times.

Inreach. Inreach will be a clinic-based implementation strategy that will consist of a referral by one's primary care provider or behavioral health team clinician at the time of a usual care visit. Eligible patients will be identified by a flag in the EHR and additionally primary care providers will be presented with orientation to the study and study referral materials in regular clinical huddles. Primary care providers will provide the same referral materials provided in the outreach condition (cover letter from clinic, culturally-tailored introduction to SilverCloud, referral for login instructions). In usual care at ZSFG, there are both 1) warm handoffs between primary care and behavioral health clinicians for mental health treatment, and 2) ongoing mental health care provided by the primary care team. In both instances of usual care, we will be able to provide hardcopy materials to enrolled providers to distribute to their panels as the study progresses. These materials will be refreshed by research staff attending regular clinical huddles on a monthly basis.

The second level of recruitment will happen once participants have enrolled in the study. They will be randomized into the unsupported dCBT or Peer-Supported dCBT.
Unsupported dCBT. Unsupported dCBT provides all features of the SilverCloud platform with the exception of the peer support (structured support from peer and share features). Patients will be provided free access to SilverCloud and instructed to use it for 8-weeks. Patients will receive weekly automated messages to encourage engagement. We have used this same strategy in our PCORI study as it is scalable and sustainable without a significant investment of resources.

Peer-supported dCBT. In the peer-supported dCBT condition, in addition to the SilverCloud platform each patient will be assigned a peer-supporter who will provide regular support based on our coaching support manual. Following our supporter protocol developed in our previous dCBT studies supporters will conduct a brief engagement call (30-40 minutes) to provide an overview of SilverCloud, identify goals and set expectations, introduce themselves, and orient the participant

to the role of the peer supporter. Supporters will then provide weekly check-ins through phone calls or messaging. The goals of weekly check-ins are to identify and resolve potential barriers outlined in the Efficiency Model (usability, engagement, knowledge, fit, and implementation) and to monitor symptom severity and progress. Participants will be able to communicate with the supporters through the platform through messaging or sharing activities for additional discussion. It is worth noting that this type of support is not conceptualized as a treatment, but rather intended to increase engagement with and impact of the evidence-based treatment, which is the dCBT platform. Therefore, although these peers will be trained with knowledge of the platform, the major goal of these peers is to promote use of the platform. Supporters will also be trained in crisis management protocols and supervised appropriately. We will monitor fidelity to the support protocol through recordings of phone calls and their use of the supporter dashboard (Aim 3a).

Peer Recruitment, Training, and Protocol. Peers will be recruited from local community organizations (Somos Esenciales) as well as from previous graduates of the BRIGHT Group Cognitive-Behavioral Therapy for Depression treatment, a 16-session group CBT treatment that has been delivered by Dr. Aguilera at ZSFG (Miranda, Woo, Lagomasino, Hepner, Wiseman, Munoz, 2006). Interested supporters will participate in 8 hours of in-person or remote training led by Drs. Aguilera, Schueller, and Kimberly Marquez-Cortes (consultant). This training will be adapted from the training we have provided to coaches in our recent coach-supported trials (Lattie, Ho, Sargent, et al., 2017; Tomasino, Lattie, Ho, Palac, Kaiser, Mohr; Mohr, Tomasino, Lattie, et al., 2017). The supporters will be trained on our coaching support protocol that details instructions for conducting an engagement phone call, monitoring participants' use of SilverCloud (i.e., the frequency, content, examples of weekly messages) and handling FAQs, crises, and escalation. The training will also include a thorough overview of SilverCloud. Each supporter will receive a guidebook that includes description of the key features of SilverCloud, the procedures for the engagement phone call and follow-up messaging, including examples of how to conduct these sessions and sample messages. During the intervention, supporters will be expected to make 1 engagement phone call at the beginning of a user's participation lasting approximately 30-40 minutes and to compose 2-3 engagement messages per week through secured messaging. Supporters will be compensated for their time dedicated to training activities and all study procedures at market rate. Supporters will also receive regular supervision. Additional supporters will be onboarded as needed due to supporter turn-over and patient recruitment. We will also have a Peer Support Advisory Committee consisting of consultants Marquez-Cortes, Camarena, Flores, and Ubozoh) that will meet quarterly to support recruitment of peers, provide guidance on the training, implementation, and evaluation of our peer-support protocol, and including interpreting our findings with a lens towards sustainability in future projects (e.g., linkage to peer support certification and payment).

Providers and peers involved in the study do not meet the definition of human subjects for this research. Peers will also receive CITI training.

For patient participants, we will review the record for PHQ-9 and GAD-7 ratings and or changes in depression or anxiety diagnosis during the time of the study.

SilverCloud Appendix attached in under other study documents

Staff at UC Berkeley have joint appointments with UCSF. UC Berkeley personnel will interact with human subjects (recruitment) and have access to identifiable data.

UCI will not interact with human subjects or any identifiable data.

7.10 * STANDARD CLINICAL PRACTICE: To what extent, if any, do the planned research procedures differ from the care that people would otherwise receive at this institution or the study site if not being done locally: (REQUIRED)

There is a standard protocol for identification, brief intervention, and referral for people who screen positive for depression and/or anxiety. However, the study site has limited Spanish speaking providers so referral is the most likely option.

7.11 * INSTRUMENTS: List all questionnaires, surveys, interview, or focus group guides that will be used for this study: (REQUIRED)

If the instruments are not complete or not available because they will be developed as part of this study, describe the basic content or include an outline and submit the final versions to the IRB with a modification for approval prior to use.

All assessments will be administered in Spanish. Online assessments will be sent first via our secure online assessment platform (REDCap79, which is made available and supported through UCSF's CTSI). Participants who fail to complete the online assessment will be provided a reminder within a one-week window before being contacted by phone with the option of completing a telephone assessment. Assessments will occur at baseline, week 8 (end-of-treatment), and at a 3-month post-treatment follow-up.

We will assess several participant characteristics including sex, age, education, acculturation, technology literacy, and previous and current use of mental health services. In addition to standard ethnicity questions, participants will be asked to indicate their national origin or ancestry, years in the US. Acculturation will be assessed by the Brief Acculturation Scale for Hispanics and by nativity status/length of time in the US. Technology literacy will be assessed using the Internet and Mobile Usage Patterns and Internet and Mobile Self-Efficacy Scales we have developed.

List of measures are as follows:
1. PHQ-9
2. GAD-7
3. Semi-Structured Interview Guide
4. Supportive accountability measure
5. Working Alliance Inventory
6. Frequency of Action and Thoughts Scale
7. Knowledge Gain in dCBT
8. Acceptability, Appropriateness, Feasibility Measure (IAM/AIM/FIM)
9. Implementation Climate Scale
10. Organizational Readiness for Change

Attach any unpublished instruments in the 'Other Study Documents' section of the Initial Review Submission Packet form after completing the study application. Published instruments should NOT be attached.

7.12 * BIOSPECIMEN COLLECTION: Are you drawing any blood or collecting other biosamples (e.g. tissue, buccal swabs, urine, saliva, hair, etc.) for analysis under this protocol and/or storage for future research: (REQUIRED)

○ Yes ◉ No

7.13 * STATISTICAL METHODS: Briefly summarize the methods and types of analyses that will be performed: (REQUIRED)

All analyses will be conducted based on intention-to-treat principles; we will use mixed-effects models adjusting for the intra-clinic correlation. Additionally, we will include participant characteristics including sex, age, education, type of Latinx group, acculturation, technology literacy, and previous use of mental health services as covariates. We will also explore baseline severity of symptoms of depression and anxiety and each peer supporter as potential moderators of treatment response.

Clinical Effectiveness (Aim 1). The primary clinical outcome for this trial is symptoms of depression and anxiety. We will compare PHQ-9 and GAD-7 scores between the conditions using mixed-effects models. Mixed-effects models generally require three time points which is why we include a post-treatment assessment at 3-months. Although every effort will be made to avoid missing data (e.g., e-mail/text reminders for assessments, financial incentives for completing

assessments), mixed-models are robust to missing data. Mixed-effects models do not require complete case data (i.e., at every time point); thus, even participants with missing data at some assessments are included in the analysis and results are modeled on the basis of the available data. In the case of missing data, we will also analyze if missing data is related to any observable characteristics. Secondary clinical outcomes for this trial will consist of the PROMIS Social Health and clinical outcome data collected from the SilverCloud platform also analyzed using mixed-effects models.

Use of Platform (Aim 1). Secondary outcomes will include measures of use as defined as time on platform. We will compare use across the two arms of the study using implementation strategy as a potential covariate (to determine if adherence differs across strategies). Mediational analysis. We will also explore whether use of the platform mediates changes in clinical symptoms. Mediation will be examined using a bootstrapping procedure (Preacher, Hayes, 2008). We will compute different models for activity from users of the platform as well as by supporters of the platform.

Implementation Outcomes (Aim 2). We will compare the proportion of patients referred, initiating, and completing treatment at each of the clinic sites using mixed-effects models using these proportions as continuous outcome variables. These models will allow us to control for intraclinic clustering of providers as well as patient characteristics of each clinic. Patient demographics and costs of treatment between arms will be compared using ANCOVAs controlling for clinic and patient characteristics.

7.14 * REFERENCES: List only the 5-10 most relevant references (a separate bibliography can be attached for reference purposes if this study involves novel approaches, agents, or an emerging technology that the IRB may not be familiar with): (REQUIRED)

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8.0 Drugs and Devices

8.1 * DRUGS AND/OR BIOLOGICS: Are you STUDYING any drugs and/or biologics that are either approved or unapproved: (REQUIRED)

○ Yes ◉ No

If you have questions about FDA requirements for drug or device research, you can send an email to request a consult.

8.3 * MEDICAL DEVICES: Are you STUDYING any medical devices, in vitro diagnostics, or assays that are either approved or unapproved:(REQUIRED)

○ Yes ◉ No

If you have questions about FDA requirements for drug or device research, you can send an email to request a consult.

9.0 Sample Size and Eligibility Criteria

9.1 * ENROLLMENT TARGET: How many people will you enroll: (REQUIRED)

426

If there are multiple participant groups, indicate how many people will be in each group:

Approximately 426 participants will be recruited to participate.

9.3 * SAMPLE SIZE JUSTIFICATION: Explain how and why the number of people was chosen. For multi-site studies, this is referring to the number that will be enrolled across all sites: (REQUIRED)

The sample size was determined based on comparisons between intervention conditions (peer-supported vs. unsupported) regarding effectiveness. With a conservative estimate based on the meta-analytic findings (Karyotaki E, Efthimiou O, Miguel C, et al., 2021) of being able to detect a two-point difference in change on the PHQ-9 or GAD-7 between treatment and control group at an α = .05, we would need 300 participants (150 per condition) to achieve power of 90%. We also estimate 25% non-use attrition (e.g., participants complete assessment measures, but do not use the platform, therefore reducing the effect) in the peer-supported group and 29% non-use attrition in the unsupported group again based on meta-analytic estimates,39 therefore our estimate of 390 total patient participants (195 per condition) would achieve excellent statistical power on Aim 1.

We have re-run our power analysis adjusting for intra-clinic and intra-provider correlations and an adjusted alpha level of = .025, assuming an ICC of 0.3 we would need 167 participants per condition to achieve 80% power or 426 total participants adjusting for our proposed attrition rate. We can update our recruitment goal from 390 (which would have had 75% power with these additional considerations) to 426 participants.

9.4 * PARTICIPANT AGE RANGE: Eligible age ranges: (REQUIRED)

- ☐ 0-6 years
- ☐ 7-12 years
- ☐ 13-17 years
- ☑ 18-64 years
- ☑ 65+

9.5 * STUDY POPULATIONS: Data will be collected from or about the following types of people (check all that apply): (REQUIRED)

- [ ] Inpatients
- [x] Outpatients
- [ ] Family members or caregivers
- [ ] Providers
- [x] People who have a condition but who are not being seen as patients
- [ ] Healthy volunteers
- [ ] Students
- [ ] Staff of UCSF or affiliated institutions
- [ ] None of the above

9.6 * SPECIAL SUBJECT GROUPS: Check the populations that may be enrolled: (REQUIRED)

- [ ] Children / Minors
- [ ] Adult subjects unable to consent for themselves
- [ ] Adult subjects unable to consent for themselves (emergency setting)
- [ ] Subjects with diminished capacity to consent
- [x] Subjects unable to read, speak or understand English
- [ ] Pregnant women
- [ ] Fetuses
- [ ] Neonates
- [ ] Prisoners
- [x] Economically or educationally disadvantaged persons
- [ ] None of the above

If not already addressed in the Background and Significance questions in the Research Plan section or elsewhere, explain why it is appropriate to include the types of subjects checked above in this particular study:

These patient's need access to quality care therefore we would like to study if technology can be used to include care to underserved public sector patients.

Consent forms will be available in both electronic and paper based forms. Electronic consent forms will be sent to participants via DocuSign. Based on our prior experience, many consent forms will come from wet signatures.

Describe the additional safeguards that have been included in the study to protect the rights and welfare of these subjects and minimize coercion or undue influence:

Here are some examples:

- evaluating capacity to consent for individuals who may be decisionally impaired (specify how)
- calibrating payment amounts to be non-coercive for the financially disadvantaged
- conducting more in-depth evaluations of subjects' understanding of the study and the voluntary nature of participation
- involving advocates in the consent process

More information and other safeguards are described here: **Vulnerable Subject Populations** and **Recruiting Staff and Students**.

We are ensuring that RA's are bilingual and can clearly communicate risks and benefits of the study. Electronic consent form and other study documents will be available and offered in the subject's primary language. Personnel will be made available and able to discuss participation in the patient's language for the consent process.

Additionally, program staff will available to provide all participants with electronic or printed information sheet that outlines the study activities and the rights of participants and will explain this information fully, allowing participants to ask questions before they decide to participate and give informed consent. All participants will be informed that they are not obligated to participate, can decline to answer questions or opt out of study activities at any time, and can leave the study at any time without threat of loss of access to any medical services to which they are normally entitled.

All participants will receive $25 for participation in these interviews regardless if they completed participation in the intervention. Compensation is enough to respect their time but not overly coercive so that it is the primary motivator.

9.7 * INCLUSION CRITERIA: Briefly describe the population(s) that will be involved in this study. Include anyone that data will be collected from or about (e.g. patients, healthy controls, caregivers, providers, administrators, students, parents, family members, etc.): (REQUIRED)

All participants must meet the following criteria:

1) PHQ-9 ≥ 10 or GAD-7 ≥ 8,

2) access to the Internet via smartphone (91% ownership in Dr. Aguilera's MoodText study and 96% in DIAMANTE study in same setting) or broadband at home, and basic level of digital literacy or willingness to undergo a digital literacy training,

3) ≥18 years of age,

4) preference for receiving medical care in Spanish,

5) not in concurrent psychotherapy and,

6) if currently taking an antidepressant medication, patient must have been on a stable dose for at least 6 weeks, and have no plans to change the dose. We will permit patients on antidepressants to enter the study, as this will increase generalizability. Antidepressant status will be assessed to control for those effects, if necessary.

9.8 * EXCLUSION CRITERIA: List any exclusion criteria (e.g. reasons why someone would not be included in the study): (REQUIRED)

1) currently receiving psychotherapy, as this treatment will be offered as a frontline treatment for depression and anxiety, however, patients are allowed to be referred to treatment while participating in this study and initiation of treatment will be monitored and considered in analyses,

2) visual, hearing, voice, or motor impairment or illiteracy that would prevent completion of study procedures,

3) diagnosis of a psychotic disorder, bipolar disorder, dissociative disorder, or substance use disorder,

4) severe suicidality (as assessed by expressing suicidal ideation, plan, and intent). Although procedures with back-up plans are in place for patients who develop suicidality, patients assessed with severe suicidality will be referred to more-intensive treatment resources.

9.9 * RESEARCH CONDUCTED ON PATIENT CARE WARDS: Do any study activities take place on any patient care units including inpatient wards, peri- or post-operative care units, operating rooms, or in the Emergency Department at UCSF Health medical facilities: (REQUIRED)

○ Yes ◉ No

9.11 * EMERGENCY DEPARTMENT: Does your protocol or study involve any of the following patient related activities in the emergency department (e.g. subject identification, recruitment, consent, blood draws, specimen retrieval, involvement of ED staff (nursing, tech, and/or physician), or any other ED based procedures): (REQUIRED)

○ Yes ◉ No

10.0 Recruitment and Consent

10.1 * COMPETITIVE ENROLLMENT: Is this a competitive enrollment clinical trial? By competitive enrollment, we mean that sites who do not enroll participants early may not get to participate at all: (REQUIRED)

○ Yes ◉ No

10.2 * SUBJECT IDENTIFICATION METHODS: What kinds of methods will be used to identify potential participants for recruitment (check all that apply): (REQUIRED)

- ☑ Review of patients' conditions, history, test results, etc. (includes patients seen in clinic, scheduled for surgery, a procedure, imaging, or tests, or seen in the Emergency Department as well as searching through medical record data for possible cohort identification)
- ☐ Already approved recruitment registry
- ☐ Re-contact of participants from the investigators' previous studies
- ☑ Referrals from colleagues (attach the 'Dear Colleague' letter or other recruitment materials you will provide to colleagues)
- ☐ Referrals from the community / word of mouth
- ☐ Advertisements (flyers, brochures, radio or t.v. ads, posting on clinical research sites or social media, presentation of the study at community events/media, etc.)
- ☐ Online recruiting tool (describe below)
- ☐ CTSI Recruitment Services unit
- ☐ Posting on UCSF Clinical Trials, ClinicalTrials.gov or other publicly available clinical trial website
- ☐ Other method (describe below)

* Provide details about the subject identification methods: **(REQUIRED)**

Outreach will be a direct-to-patient implementation strategy that will leverage the patient registry at ZSFG. This registry is based on patient- and provider-reported data and demographics in the Epic electronic health record (EHR). Registry reports can be pulled based on validated population health management tools in Epic, specifically the Healthy Planet tool. These reports include patient demographics and primary care provider problem list diagnoses and visit diagnoses and any structured assessment data including PHQ-9 (Patient Health Questionnaire-9) and/or GAD-7 (Generalized Anxiety Disorder 7). Thus, preference for Spanish, a diagnosis of depression or anxiety on the problem list or visit summary or PHQ-9 and/or GAD-7 scores will all be available on these reports. In the outreach strategy, potentially eligible patients will be identified and contacted.

First mode of contact will be through a letter presenting the study, sent on behalf of the research team by the patient's clinic, providing information about how to opt out of further contact, prior to phone contact by the research team.

Inreach will be a clinic-based implementation strategy that will consist of a referral by one's primary care provider or behavioral health team clinician at the time of a usual care visit. Eligible patients will be identified by a flag in the EHR and additionally primary care providers will be presented with orientation to the study and study referral materials in regular clinical huddles.

Primary care providers will provide the same referral materials provided in the outreach condition (cover letter from clinic, culturally-tailored introduction to SilverCloud, referral for login instructions).

10.3 * SEARCHING OF MEDICAL RECORDS: (REQUIRED)

Whose patients are they:

- [x] Investigators' own patients or patients seen within the same practice
- [x] Patients not under the care of the investigators

How and by whom will records be accessed and searched (check all that apply):

- [ ] Self-search in APeX or other medical records source
- [ ] Self-search using UCSF's Research Cohort Selection Tool
- [ ] CTSI Consultation Service Recruitment Services
- [ ] UCSF Academic Research Services (ARS)
- [ ] University of California Research Exchange (UC ReX)
- [x] Other method (describe below)

Describe the other ways medical records may be accessed and searched to identify prospective participants:

To determine eligibility of patients participating, research staff will generate through the electronic health record lists of patients meeting the following criteria: patients at RFPC or FHC; Spanish-speaking; age 18+; PHQ-9 ≥ 10 or GAD-7 ≥ 8. A study team member will contact PCPs with a list of their patients eligible for inclusion to seek their approval to recruit patients and will then contact eligible patients to offer the intervention. Additionally, patients identified as eligible through the registry will receive a flag in the EHR so that the provider can introduce the study to them, and for providers who are randomly assigned to the "inreach" condition any patient of the providers in this condition may be referred for dCBT by their PCP or corresponding behavioral health clinician and our team will confirm eligibility.

10.4 * DETERMINATION OF ELIGIBILITY: How, when, and by whom will eligibility for recruitment be determined: (REQUIRED)

To determine eligibility of patients participating, research staff will generate through the electronic health record lists of patients meeting the following criteria: patients at RFPC or FHC; Spanish-speaking; ≥18 years of age; PHQ-9 above 10 or GAD-7 above 8. Potential participants will be contacted either by the inreach or outreach strategy. For participants whose providers are assigned to outreach, we will receive monthly reports using the registry to identify positive depression (PHQ or depression diagnosis) and anxiety (GAD or anxiety diagnosis) screens. For participants whose providers are assigned to inreach we will provide monthly reminders to providers including reports on the numbers of patients referred and enrolled.

Providers' assessment of eligibility will be limited to a general initial assessment of potential eligibility based on the list provided and their knowledge of the patients, and the research team will be responsible for confirming the full eligibility criteria once the provider has referred a potential participant to them. Staff will then contact patients via phone or in-person in the clinics to assess additional eligibility criteria, including access to the Internet via smartphone or broadband at home, basic level of digital literacy or willingness to undergo a digital literacy training, preference for receiving medical care in Spanish, not in concurrent psychotherapy and, if currently taking an antidepressant medication, patient must have been on a stable dose for at least 6 weeks, and have no plans to change the dose. We will permit patients on antidepressants to enter the study, as this will increase generalizability. Antidepressant status will be assessed to control for those effects, if necessary.

10.5 * INITIATION OF CONTACT: Who initiates contact (check all that apply): (REQUIRED)

- [x] Investigators/study team
- [ ] UCSF recruitment unit (e.g. CTSI Consultation Services)
- [ ] Potential participant
- [x] Other (explain below)

Provide details about how contact is initiated:

First mode of contact will be through a letter presenting the study, sent on behalf of the research team by the patient's clinic, providing information about how to opt out of further contact, prior to phone contact by the research team.

Trained research staff will recruit patients via phone who meet eligibility (out-reach). Eligible patients flagged in the EHR will be introduced and referred to the study by their provider (in-reach).

10.6 * HOW IS CONTACT INITIATED: (check all that apply): (REQUIRED)

- [x] In person
- [x] Phone
- [ ] Letter / email
- [ ] Website or app
- [ ] Other (explain below)

Attach the telephone recruitment script in the Other Study Documents section of the Initial Review Submission Packet Form. If potential participants will initiate contact, attach the telephone screening script that will be used to provide more information about the study and determine if callers are eligible to participate.

10.7 RECRUITMENT PLAN: Based on the checkboxes you chose above, please provide a narrative describing your recruitment plan. We want to know:

- **Who is conducting the search for potential participants, and how?**
- **How are potential subjects being approached for recruitment? By whom, and when?**

If there will be more than one participant group (e.g. patients, healthy controls, caregivers, family members, providers, etc.), provide details about the recruitment plans for each group. (Recommended length - 100-250 words)

Provider pre-approved list will be sent to recruitment team. After assessing eligibility via chart review, trained research staff will contact patients via phone. Outreach phone call will provide an introduction to SilverCloud. These phone calls will be followed by a video call orientation or a letter from the clinic, culturally-tailored introduction to SilverCloud, and a referral to receive login instructions.

For providers who are randomly assigned to the "inreach" condition any patient of the providers in this condition may be referred for dCBT by their PCP or corresponding behavioral health clinician and our team will confirm eligibility.

10.8 * CONSENT METHODS: How will permission to participate (i.e., informed consent) be obtained from each potential participant. If there will be multiple groups and different plans for consenting each, check all that apply. See the orange Help bubble to the right for more detailed guidance. Participants will (check all that apply): (REQUIRED)

- [x] Sign a paper consent form at the end of the consent discussion (signed consent)
- [x] Sign an electronic consent form using DocuSign or REDCap's e-signature function (signed consent)
- [ ] Provide online unsigned consent through an app, a website, or a survey tool such as Qualtrics or REDCap (waiver of signed consent)
- [ ] Be told about the study and be given a handout/information sheet and be asked if they agree to participate (verbal consent - waiver of signed consent)
- [ ] Complete the study activities and turn in materials, as in the case of a completed survey that is placed in a drop box or mailed to the study team (implied consent - waiver of signed consent)
- [ ] Not be able to provide consent and will have a family member consent for them, as in the case of a critically ill or unconscious patient (surrogate consent)
- [ ] Not able to provide consent (emergency medicine, greater than minimal risk waiver/alteration of consent - requires an approved community consultation plan)
- [ ] Not able to provide consent (emergency medicine, minimal risk waiver/alteration of consent)
- [ ] Not know about the study, as in the case of chart reviews or observations of public behavior (waiver of consent)
- [ ] Other method (describe below)

Attach your consent form, information sheet, or electronic consent text in the Informed Consent Documents section of the Initial Review Submission Packet Form.

Use of the FDA-compliant (also called "Part 11 Compliant") version of DocuSign and REDCap is recommended for research consent.
To use FDA-compliant DocuSign, submit an access request at https://ucsf.service-now.com/ucsfit and contact it-cloudapps@ucsf.edu with questions. For the FDA-compliant version of REDCap ("REDCap Premium"), go to https://redcap-prem.ucsf.edu and contact Academic Research Systems Support with questions. More information on electronic consent options for research is available online in FAQ #2.

10.9 * CONSENT PROCESS: Describe the process for obtaining informed consent, including details such as who will have the consent discussion and when participants will be asked to sign the consent form in relation to finding out about the study: (REQUIRED) We encourage researchers to review our guidance on obtaining and documenting informed consent.

- **If there are multiple groups being consented differently, provide details about the consent process for each group.**
- **If you are relying on verbal or implied consent, provide details about how that will happen.**
- **For studies using online recruitment and consent or consent via mail, provide details here.**

Patients will be given an opportunity to read through the consent form and HIPAA form, and study personnel will review the forms with them. Patients can ask any questions they have then. Once their concerns have been clearly addressed, they will be asked to explain their understanding of the purpose of the study and what they will be asked. If they understand the study procedures and are still comfortable with participating, they will be asked to sign the written consent form and HIPAA form. If they do not seem to fully understand the study procedures, we will continue reviewing the procedures with them and clarify any questions.

Consent forms will be available in both electronic and paper based forms. Electronic consent forms will be sent to participants via DocuSign. Based on our prior experience, many consent forms will come from wet signatures.

* It is important that the people obtaining consent are qualified to do so. Briefly describe the training and experience these individuals have in obtaining informed consent: **(REQUIRED)**

Research staff have experience and training obtaining consent in different research studies. Additional training specific to this study will ensure research staff are qualified to obtain informed consent. All staff possess CITI training.

10.10 * CONSENT COMPREHENSION: Indicate how the study team will assess and enhance the subjects' understanding of study procedures, risks, and benefits prior to signing the consent form (check all that apply): (REQUIRED) Tip: Review the Consent Comprehension - Learning Notes in the Help bubble at the right for specific questions that can be asked to assess comprehension, consider using the UCSF Decision-Making Capacity Assesment Tool, and review our guidance on obtaining written or verbal informed consent for more detail on how to conduct the assessment.

- [x] The study team will engage the potential participant in a dialogue, using open-ended questions about the nature of the study or the experimental treatment, the risks and benefits of participating, and the voluntary nature of participation
- [ ] Potential participants will be asked or shown a series of questions to assess their understanding of the study purpose, procedures, risks and benefits, as well as the voluntary nature of participation (especially appropriate when the consent process happens online or through a mobile health app)
- [ ] Other method (describe below):

Provide details of the other approaches that will be used, if using another method to assess comprehension:

10.11 * DECEPTION: Does this study rely on some deception or misinformation about what the researchers are observing to get valid data? (REQUIRED)

- ( ) Yes
- (•) No

10.12 * NON-ENGLISH CONSENT METHOD: Indicate which method(s) you will use to consent non-English speaking subjects: (REQUIRED)

- [x] Preferred Method—Consent form and other study documents will be available in the subject's primary language Personnel able to discuss participation in the patient's language will be present for the consent process.
- [ ] Short-Form—A qualified interpreter will translate the consent form verbally, and subjects will be given the Experimental Subject's Bill of Rights in their primary language, following instructions in Those Who do not Read, Speak or Understand English for required witnessing and signatures

* Explain how you will maintain the ability to communicate with non-English speakers throughout their participation in the study: **(REQUIRED)**

Clinicians and study researchers are bilingual/bicultural. Enrollment materials will be available in Spanish.

10.14 TIME: What is the estimated time commitment for participants (per visit and in total):

Participants will come in for a pre and post interviews that will each take approximately 45-60 minutes each. The time commitment during the study will vary by participant's level of engagement. There are multiple exercises that can be completed on the app, and participants will

have the option to use it as desired. We estimate the minimum amount of time spent would be 35 minutes [per week] or 1 hour [per week] for those receiving peer support. Participants can spend more time on the app if desired.

During the intervention, supporters will be expected to make 1 engagement phone call at the beginning of a user's participation lasting approximately 30-40 minutes and to compose 2-3 engagement messages per week through secured messaging.

Trial participants will be in the study for 20 weeks. 8 weeks in the dCBT and will receive a 3-month follow up.

IMPORTANT TIP: Ensure this information is consistent with the information provided in the consent form.

10.15 ALTERNATIVES: Is there a standard of care (SOC) or usual care that would be offered to prospective participants at UCSF (or the study site) if they did not participate in this research study:

(•) Yes ( ) No

Describe the care that patients would ordinarily receive at the medical center if they did not participate in this study (provide details, assuming that some of the IRB members are not specialists in this field):

Patient will continue to receive their usual care with their primary care provider

10.16 OFF-STUDY TREATMENT: Is the study drug or treatment available off-study:

( ) Yes
(•) No
( ) Not applicable

10.17 OTHER ALTERNATIVES: Describe other alternatives to study participation, if any, that are available to prospective subjects:

Participants will be able to choose whether or not to participate in the study and will receive treatment as usual.

11.0 Waiver of Consent/Authorization for Recruitment Purposes

This section is required when medical records may be reviewed to determine eligibility for recruitment.

11.1 * PRACTICABILITY OF OBTAINING CONSENT PRIOR TO ACCESS: Study personnel need to access protected health information (PHI) during the recruitment process and it is not practicable to obtain informed consent until potential subjects have been identified: (REQUIRED)

(•) Yes

If **no**, a waiver of consent/authorization is NOT needed.

11.2 * RISK TO PRIVACY: A waiver for screening of health records to identify potential subjects poses no more than minimal risk to privacy for participants:

(•) Yes

If **no**, a waiver of authorization can NOT be granted.

11.3 * RIGHTS/WELFARE: Screening health records prior to obtaining consent will not adversely affect subjects' rights and welfare:

(•) Yes

If **no**, a waiver of authorization can NOT be granted.

11.4 * IDENTIFIERS: Check all the identifiers that will be collected prior to obtaining informed consent:

- [x] Names
- [x] Dates
- [ ] Postal addresses
- [x] Phone numbers
- [ ] Fax numbers
- [x] Email addresses
- [ ] Social Security Numbers*
- [x] Medical record numbers
- [ ] Health plan numbers
- [ ] Account numbers
- [ ] License or certificate numbers
- [ ] Vehicle ID numbers
- [ ] Device identifiers or serial numbers
- [ ] Web URLs
- [ ] IP address numbers
- [ ] Biometric identifiers
- [ ] Facial photos or other identifiable images
- [ ] Any other unique identifier
- [ ] None

Note: HIPAA rules require that you collect the minimum necessary.

11.5 * HEALTH INFORMATION: Describe any health information that will be collected prior to obtaining informed consent:

In order to screen patients for eligibility for recruitment, charts will be reviewed for medical diagnosis or clinical notes of depression and/or anxiety.

Note: HIPAA requires that you collect the minimum necessary.

11.6 * DATA RETENTION/DESTRUCTION PLAN: Describe your plan to destroy any identifiable data collected to determine eligibility for recruitment. This should be done at the earliest opportunity. If you plan to retain identifiable recruitment data, provide the justification for doing so:

Screening of health records will yield a list of patients eligible for recruitment. This list will be stored with a password on a secure UCSF network and will only be accessed by study staff. Identifiable data from this list will be deleted from the computer after eligibility is determined for each patient.

12.0 Risks and Benefits

12.1 RESEARCH-RELATED RISKS: Check if your study involves any of these specific research-related risks to participants that may need to be disclosed in the consent form:

- [ ] Physical discomforts or pain
- [ ] Risks to employment, or social or legal standing
- [x] Risk that the study team may observe possible evidence of child abuse, elder abuse, or a threat to self or others that they are required to report

For reportable information, include details of the reporting plan below. (See the Help link for Mandated Reporter child and elder abuse resources.)

* For any boxes checked above, describe how you will minimize these risks and discomforts, e.g., adding or increasing the frequency of monitoring, additional screening to identify and exclude people with diminished kidney or liver function, or modification of procedures such as changing imaging studies to avoid giving contrast agent to people who are more likely to suffer side effects from it, etc.: **(REQUIRED)**

Risks associated with research assessments: All responses to assessment questions are voluntary; participants are told that they can decline to answer any questions that they choose and are under no obligation to answer any questions they are not comfortable with. The instruments and methodologies are well-tested and are not known to cause problems or distress on the part of the participants. In this trial, participants will answer the PHQ item 9 which addresses thoughts of death or self-harm. If participants indicate a value > 0, they will receive a list of crisis support services within the assessment or SilverCloud platform (which is consistent with the safety monitoring plan of SilverCloud), and the PIs (Dr. Schueller and Dr. Aguilera) will receive an automated message that will be addressed within 24 hours. A study assessor will contact the participant to complete a suicide risk assessment will be conducted using the Columbia-Suicide Risk Assessment. In addition, the assessor will assess for support plan and level of imminence. If participant level of risk is assessed as severe the assessor will alert the clinical supervisor (Dr. Aguilera or assigned clinical supervisor), explain duty-of-care to participant, and follow a guided crisis procedure protocol.

The crisis procedure protocol involves:

(1) restating duty of care,

(2) confirming landline and mobile number,

(3) confirming address and current location,

(4) contact the clinical supervisor/team leader,

(5) call 911 emergency services,

(6) keep participant on phone and engaged until police arrive,

(7) complete documentation.

Participants who do not report imminent risk but indicated a > 0 score on the PHQ item 9 will be provided a list of resources drawn from ZSFG. This risk assessment will be supervised by a member of clinical staff on the research team, and appropriate referrals and resources provided as needed as described. This is consistent with the risk monitoring procedures we are using in our current clinical trial (R34 MH113616, PI: Schueller). Supporters will also be trained on a similar crisis management protocol, but will learn to assess for level of risk themselves so will only need

to contact the clinical supervisor immediately in assessment of high level of risk but will also complete a report indicating any risk assessed that will be provided to the clinical supervisor for review and sign-off with 24 hours.

12.2 * RISKS: Describe any anticipated risks and discomforts not listed above: (REQUIRED)

Risks of the intervention: Digital mental health intervention programs generally have not been shown to cause harm. We do not expect that this intervention creates an added risk for suicidal ideation.

Risks associated with research assessments: Research assessments include questions about depression, anxiety, and other mental and emotional problems. There is a risk that responding to these assessments may cause some level of distress discomfort to participants.

Risk of delayed treatment: By participating in this study and using SilverCloud, it is possible some people may delay care that might otherwise be effective, resulting in additional distress or potential further impairment that might make later treatment more challenging. However, given that lack of Spanish speaking providers, this is unlikely. It is also possible that a participant might try a technology, not receive any benefit, and be less likely to seek subsequent care due to the belief that it might not be effective. Patients who are currently taking antidepressant medication will be eligible to participate, if they are on a stable dose for at least 6 weeks. Patients who are currently engaged in psychotherapy will not be eligible, however participants will be allowed to be referred to psychotherapy will participating which will mitigate concerns with risks of delaying treatment.

Risks associated with potential loss of confidentiality/privacy: There is a slight risk of loss of confidentiality or privacy. There is some possibility that others in the participants' lives may see the participant's app notifications. There is also a small possibility that databases may be hacked, even though they are behind secure firewalls. Confidentiality may be broken by research staff to ensure the participant's safety if they identify an imminent threat to self or others. There is also the remote possibility that research records will be subpoenaed by a court of law.

Randomization to an inferior outcome depending on group assignment: We can't speak for sure about inferior outcomes which is why we don't think it's appropriate to state here.

Risk of data charges: There could be some additional data charges as a result of the SilverCloud app usage by the participants' phone provider.

12.3

MINIMIZING RISKS: Describe the steps you have taken to minimize the risks/discomforts to subjects. Examples include:

- **designing the study to make use of procedures involving less risk when appropriate**
- **minimizing study procedures by taking advantage of clinical procedures conducted on the study participants**
- **mitigating risks by planning special monitoring or conducting supportive interventions for the study**
- **having a plan for evaluation and possible referral of subjects who report suicidal ideation**

Risks of the intervention: Upon enrollment, participants will be instructed to report any unanticipated consequence of using the digital intervention to study staff. We will monitor any unanticipated consequences on outcome assessments.

Risk of delayed treatment: We will explain to participants in the study information sheet that these apps are not intended to replace professional care and encourage participants to always speak to licensed professionals if they are experiencing distress or need professional support.

Risks associated with potential loss of confidentiality/privacy: All of potential losses of confidentiality will be disclosed in the consent documents. SilverCloud collects data in accordance with the EU General Data Protection Regulation (GDRP), the Data Protection Act 2018 and other applicable data protection and e-privacy law. REDCap is a secure online assessment platform, made available and supported through UCSF's CTS. Data gathered by SilverCloud includes responses to the CBT assignments, IP address, unique identifiers, browser type and version, time zone and language, country, pages viewed. Although highly unlikely to occur, loss of privacy

would reveal PHQ-9, GAD-7, interaction with the SilverCloud platform, IP addresses and browsing behavior. Further, peer supporters will interact with patients either through brief phone calls or secure messaging

To ensure that confidentiality is maintained throughout the study, only secure software and tools will be used for data collection. Each participant will be given a unique numeric identifier (different from their name or medical record number) that will be affixed to any research material associated with the patient. This information will be kept in a password-protected file on a UCSF server; only study staff will have access to this file. Only the researchers and industry partner support staff will have access to data stored on the respective app servers. When analyses have been completed and all research potential exhausted, these records will be destroyed. Any paper documentation (which we do not anticipate) is kept in locked file cabinets or a locked file room.

All research team members will be trained in data security and will need to sign an official university confidentiality document prior to being granted access to confidential files. All analyses reported from this study will only contain aggregate data. The data from individual participants may be reported, anonymously, as examples of participant feedback.

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Data collected by the SilverCloud platform created for this project will be encrypted and stored on the SilverCloud online server. When the data are transmitted to our local server at UCSF, we use commercial-grade HTTPS encryption to secure the contents of the network transmission. Furthermore network payloads are further protected using public-key cryptography to encrypt the data so that only the intended server may decode the contents of the transmission, even in cases where the transport layer encryption (HTTPS) may be compromised.

12.5 * BENEFITS: (REQUIRED) Note: These are the benefits that the IRB will consider during their review. They are not necessarily appropriate to include in the consent form.

Possible immediate and/or direct benefits to participants and society at large (check all that apply):

- [x] Positive health outcome (e.g. improvement of condition, relief of pain, increased mobility, etc.)
- [x] Closer follow-up than standard care may lead to improved outcomes or patient engagement
- [x] Health and lifestyle changes may occur as a result of participation
- [x] Knowledge may be gained about their health and health conditions
- [x] Feeling of contribution to knowledge in the health or social sciences field
- [ ] The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children
- [x] Other benefit (describe below)
- [ ] None

Briefly discuss the other possible benefits:

Potential benefits of the study to safety-net setting and primary care clinics include the improvement of best practices in digital mental health for LEP Latinx populations. This important step is improving care for vulnerable populations, because of the lack of mental health professionals to meet the burden of disorder for depression and anxiety, especially for underrepresented populations like Latinx. We need new interventions that can be deployed at scale in low-resource settings and meet the needs of individuals for diverse groups.

Participants may benefit from the CBT intervention and will notice a reduction in depression and anxiety scores.

12.6 RISK TO BENEFIT RATIO: Explain why the risks to subjects are reasonable in relation to anticipated benefits, if any, to the participant or society:

Risks in the study are only slightly if at all greater than standard care. We have also attempted to address any risks with various safeguards.

12.7 * DATA AND SAFETY MONITORING: Do you have a Data and Safety Monitoring Plan (DSMP) for this study (A DSMP is required for Greater than Minimal Risk research): (Click the Help link for guidance on risk determination) (REQUIRED)

(•) Yes ( ) No

This is not required for minimal risk research but the UCSF IRB strongly recommends one to ensure the data collected are adequate to meet the research aims:

13.0 Data and Safety Monitoring Plan

13.1 * DATA AND SAFETY MONITORING PLAN (DSMP): (REQUIRED) Provide a summary of the DSMP:

All greater than minimal risk studies are required to provide a plan. Lack of an adequate plan is one of the most common reasons why IRB approval is delayed.

Instructions:

Describe the plan for monitoring data quality and participant safety. Key areas that should be included in the plan are:

- An explanation of the plan to monitor data collection, study progress, and safety
- A description of who will perform the monitoring and at what frequency (e.g., the PI only, a contract research organization, a Data and Safety Monitoring Board or Data Monitoring Committee, etc.)
- The type of data and events that will be reviewed (e.g., adverse events, breaches of confidentiality, unanticipated problems involving risk to participants or others, unblinded efficacy data, etc.)
- Procedures and timeline for communicating monitoring results to the UCSF IRB, the study sponsor, and other appropriate entities

As appropriate:

- A plan for conducting and reporting interim analysis
- Clearly defined stopping rules
- Clearly defined rules for withdrawing participants from study interventions

To ensure that confidentiality is maintained throughout the study, only secure software and tools will be used for data collection. Each participant will be given a unique numeric identifier (different from their name or medical record number) that will be affixed to any research material associated with the patient. This information will be kept in a password-protected file on a UCSF server; only study staff will have access to this file. Only the researchers and industry partner support staff will have access to data stored on the respective app servers. When analyses have been completed and all research potential exhausted, these records will be destroyed. Any paper documentation (which we do not anticipate) is kept in locked file cabinets or a locked file room.

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Any reportable post-approval research-related event or information will be communicated to the IRB in accordance with the IRB's **post-approval reporting requirements**.

13.2 * DATA AND SAFETY MONITORING BOARD (DSMB): (REQUIRED) Will a Data and Safety Monitoring Board (DSMB) be established:

- ○ Yes
- ◉ No

Guidelines

A Data and Safety Monitoring Board (DSMB) or Data Monitoring Committee (DMC) is a formal, independent committee that is specifically established to conduct interim monitoring, oversight and analysis of study information and data to assure the continuing safety, efficacy, appropriateness, relevance, and integrity of the study.

The UCSF IRB reserves the right to request a DSMB/DMC for any study. However, the following are factors that the IRB will consider when making this determination:

- There is a significant likelihood of a serious adverse event to subjects
- The study is conducted at multiple sites and the level of risk is greater than minimal
- The study generates data that are blinded or randomized
- The study involves a large number of patients randomized to one of two or more interventions
- A study for which the performance of an interim analysis is crucial for the protection of the subjects
- First use in humans
- First use in children
- The study involves gene therapy, stem cell therapy, or other novel interventions for which long-term outcome data are not known or available

14.0 Confidentiality, Privacy, and Data Security

14.1 * PROTECTING PRIVACY: Indicate how subject privacy will be protected: (REQUIRED)

- ☑ Conduct conversations about the research in a private room
- ☑ Ask the subject how they wish to be communicated with – what phone numbers can be

called, can messages be left, can they receive mail about the study at home, etc.

☐ Take special measures to ensure that data collected about sensitive issues do not get added to their medical records or shared with others without the subject's permission

☐ Other methods (describe below)

14.2 * SENSITIVE DATA: Do any of the instruments ask about illegal or stigmatized behavior: (REQUIRED)

○ Yes ◉ No

14.3 * SIGNIFICANT CONSEQUENCES OF A LOSS OF PRIVACY OR CONFIDENTIALITY: Could a breach of privacy or confidentiality result in any significant consequences to participants, such as criminal or civil liability, loss of state or federal benefits, or be damaging to the participant's financial standing, employability, or reputation: (REQUIRED)

○ Yes ◉ No

14.4 EXTRA CONFIDENTIALITY MEASURES: Explain any extra steps that will be taken to assure confidentiality and protect identifiable information from improper use and disclosure, if any:

14.5 * REPORTABILITY: Do you anticipate that this study may collect information that State or Federal law requires to be reported to other officials, such as elder abuse, child abuse, or threat to self or others, or HIV status and other reportable conditions: (REQUIRED)

◉ Yes ○ No

The confidentiality and privacy section of the consent form must include this as a possible risk of participation.

* Describe the types of reportable information the research team may encounter and provide the details of the reporting plan: **(REQUIRED)**

If patients report that they are in danger of harming themselves or others or if they report instances of child or elder abuse, these things are reportable. They are informed of this at the beginning of the study and as a standard protocol.

14.6 * CERTIFICATE OF CONFIDENTIALITY: Will this study obtain a Certificate of Confidentiality: (REQUIRED)

◉ Yes ○ No

NOTE: if your study is federally funded and collects personally identifiable information, it will automatically be issued a Certificate of Confidentiality. You must include the required Certificate of Confidentiality language in the consent form.

14.7 * SHARING OF RESEARCH RESULTS: Will there be any sharing of EXPERIMENTAL research test results with subjects or their care providers: (REQUIRED)

○ Yes ◉ No

14.9 * HIPAA APPLICABILITY: Study data will be: (REQUIRED)

- [x] Derived from a medical record (e.g. APeX, OnCore, etc. Identify source below)
- [ ] Added to the hospital or clinical medical record
- [x] Created or collected as part of health care
- [ ] Used to make health care decisions
- [x] Obtained from the subject, including interviews, questionnaires
- [ ] Obtained ONLY from a foreign country or countries
- [ ] Obtained ONLY from records open to the public
- [ ] Obtained from existing research records
- [ ] None of the above
- [ ] Derived from the Integrated Data Repository (IDR) or The Health Record Data Service (THREDS) at ZSFG

In addition to signing a consent form, each subject will have to sign the UCSF Participant Authorization for Release of PHI for Research (HIPAA Form). Upload the HIPAA Form in the Other Study Documents section of the Initial Review Submission Packet Form. Failure to have patients sign the HIPAA Authorization is one of the most common findings from QIU Routine Site Visits.

Guidance about HIPAA requirements and other HIPAA-related forms are available online on the IRB's HIPAA page.

If derived from a medical record, identify source (UCSF Health APeX, SFDPH Epic, VA CPRS, etc.):

EPIC

14.10 * GDPR APPLICABILITY: Answer the following questions to determine if this study is subject to additional data privacy regulations under the General Data Protection Regulation (GDPR and/or UK GDPR): (REQUIRED)

* Is the study targeting or recruiting **European Economic Area (EEA)** or United Kingdom (U.K.) participants, or collecting and using the personal data of participants located in the EEA or the U.K.: **(REQUIRED)**

NOTE: If this study is being carried out online and may recruit people living in the EEA zone or the U.K., you should check 'Yes.'

( ) Yes (•) No

* Is the study receiving data from a site that is collecting data from individuals located in the EEA or U.K. nations: **(REQUIRED)**

( ) Yes (•) No

14.11 * IDENTIFIERS: Will any of the following identifiers be collected and included in the research records, even temporarily: (REQUIRED)

- [x] Names
- [x] Dates
- [x] Postal addresses (if only requesting/receiving zip codes check Yes to the Zip Code question below instead of checking this box)
- [x] Phone numbers
- [ ]

- [ ] Fax numbers
- [x] Email addresses
- [ ] Social Security Numbers*
- [x] Medical record numbers
- [ ] Health plan numbers
- [ ] Account numbers
- [ ] License or certificate numbers
- [ ] Vehicle ID numbers
- [ ] Device identifiers or serial numbers
- [ ] Web URLs
- [ ] IP address numbers
- [ ] Biometric identifiers
- [ ] Facial photos or other identifiable images
- [ ] Any other unique identifier
- [ ] None

* Could study records include *ANY* photos or images (even 'unidentifiable' ones): **(REQUIRED)**

- ( ) Yes
- (•) No

14.13 * PATIENT MEDICAL RECORDS: Will health information or other clinical data be accessed from UCSF Health, Benioff Children's Hospital Oakland, or Zuckerberg San Francisco General (ZSFG): (REQUIRED)

- (•) Yes
- ( ) No

14.16 * HIPAA - PERMISSION TO ACCESS SENSITIVE DATA: Does the research require access to any of the following types of health information from the medical record: (check all that apply) (REQUIRED)

- [ ] Drug or alcohol abuse, diagnosis or treatment
- [ ] HIV/AIDS testing information
- [ ] Genetic testing information
- [x] Mental health diagnosis or treatment
- [ ] None of the above

Important note: Ensure that participants initial the corresponding line(s) in Section C of the HIPAA authorization form during the consent process.

14.20 * DATA COLLECTION AND STORAGE: (check all that apply): (REQUIRED)

Collection methods:

- [ ] Electronic case report form systems (eCRFs), such as OnCore or sponsor-provided clinical trial management portal
- [x] UCSF ITS approved Web-based online survey tools: Qualtrics or RedCap
- [ ] Other web-based online surveys or computer-assisted interview tool
- [x] Mobile applications (mobile or tablet-based)
- [ ] Text Messaging
- [ ] Wearable devices
- [x] Audio/video recordings
- [ ] Photographs
- [x] Paper-based (surveys, logs, diaries, etc.)

☐ Other:

* What online survey or computer assisted interview tool will you use: **(REQUIRED)**

☑ Qualtrics (Recommended)
☑ RedCAP (Recommended)
☐ Survey Monkey (NOT recommended and may require UCSF ITS Security review)
☐ Other

* For each app and device, please provide: **(REQUIRED)**

- the name of the mobile application or wearable device
- name of the manufacturer / application owner
- the FDA status (required for mobile health applications and mobile health devices)

Patients will be introduced to SilverCloud, a web and mobile platform that can be accessed through computers and smartphones. SilverCloud delivers online CBT. Developed by SilverCloud Health, Owned by Amwell, SilverCloud falls under the category of apps which FDA has exercised enforcement discretion over so the FDA status is not applicable

* Data will be collected/stored in systems owned by (check all that apply): **(REQUIRED)**

☐ Study sponsor
☑ UCSF data center (including OnCore, RedCap, Qualtrics, and MyResearch)
☑ UCSF encrypted server, workstation, or laptop residing outside of UCSF data center
☐ Personal devices, such as laptops or tablets that are not owned or managed by UCSF
☐ San Francisco VA Health Care System (SFVAHCS)
☑ Zuckerberg San Francisco General Hospital
☐ Benioff Children's Hospital Oakland
☐ Langley Porter Psychiatric Institution
☐ Other UCSF affiliate clinic or location (specify below)
☐ Cloud vendor such as Amazon Web Services (AWS), Salesforce, etc. (specify below)
☐ Other academic institution
☐ 3rd party vendor (business entity)
☑ Other (explain below)

* Provide more details about where study data will be stored: **(REQUIRED)**

Data will only be stored on UCSF Box. Participants data will be stored on SilverCloud servers.

14.21 * ADDITION OF RECORDS TO A REGISTRY: Will patient records reviewed under this approval be added to a research database, repository, or registry (either already existing or established under this protocol): (REQUIRED)

○ Yes ◉ No

14.22 * DATA SHARING: During the lifecycle of data collection, transmission, and storage, will identifiable information be shared with or be accessible to anyone outside of UCSF: (REQUIRED)

◉ Yes ○ No

* Who will have access to the data: **(REQUIRED)**

☑ Collaborators listed in the study application

- [ ] NIH or other shared data repository
- [ ] Sponsors
- [ ] FDA
- [x] Other 3rd party (such as vendors/contractors)

IMPORTANT: The IRB now recommends that all consent forms include a provision for sharing of de-identified/coded data to permit re-use of data for secondary research purposes. This doesn't apply if you've been granted a waiver of consent for this study.

* Provide the details of whom the data will be shared with and what types of information and identifiers will be shared: **(REQUIRED)**

Users will have to make a login so SilverCloud will have their email addresses, we'll also share identified data between the UCSF and UCI teams

14.23 * DATA SHARING METHODS: How will data be securely shared with the 3rd party: (REQUIRED)

- [ ] Collaborators will access data in MyResearch
- [ ] Collaborators will access data in REDCap
- [x] Collaborators will be sponsored as an affiliate and be treated as an UCSF user (includes using UCSF Box)
- [ ] UCSF Secure Email will be used to share data
- [ ] Collaborator's or Sponsor's system will be used (specify below)
- [x] Other method (describe below)

Please provide details about how the data will be shared:

Secured box folders will be shared with collaborators.

Data will also be securely shared via the SilverCloud platform.

15.0 Financial Considerations

15.1 * PAYMENT: Will subjects be paid for participation or receive any other kind of compensation: (REQUIRED)

(•) Yes ( ) No

15.2 * REIMBURSEMENT: Will participants be reimbursed for expenses related to study participation: (REQUIRED)

( ) Yes (•) No

15.3 * PAYMENT/REIMBURSEMENT METHODS: Participant payment or compensation methods (check all that apply): (REQUIRED)

Payments will be (check all that apply):

- [x] Cash
- [ ] Check
- [x] Gift card
- [ ] Debit card
- [ ] UCSF Research Subject Payment Card
- [ ] Reimbursement for parking and other expenses
- [ ] Other:

15.4 * PAYMENT SCHEDULE: Describe the schedule and amounts of payments, including the total subjects can receive for completing the study: (REQUIRED)

- **If there are multiple visits over time, explain how payments will be prorated for partial completion**
- **If deviating from recommendations in Subject Payment Guidelines, include specific justification below**

Patients will be recruited by direct contact from our research team or referrals from providers. All participants will receive $25 for participation in interviews regardless if they completed participation in the intervention in the form of either gift card (Amazon) or cash.

15.5 * COSTS TO SUBJECTS: Will subjects or their insurance be charged for any study activities: (REQUIRED)

○ Yes ◉ No

16.0 Other Approvals and Registrations

16.4 OTHER APPROVALS: Indicate if this study involves other regulated materials and requires approval and/or authorization from the following regulatory committees:

☐ Institutional Biological Safety Committee (IBC)

Specify BUA #:

☐ Institutional Animal Care and Use Committee (IACUC)

Specify IACUC #:

☐ Controlled Substances

17.0 Qualifications of Key Study Personnel and Affiliated Personnel

NEW: January 2019 - Affiliated personnel who do not need access to iRIS no longer need to get a UCSF ID. Instead, add them below in the Affiliated Personnel table below.

17.1 Qualifications of Key Study Personnel:

Instructions:

For UCSF Key Study Personnel (KSP)* listed in **Section 3.0,** select the KSP from the drop down list and add a description of their study responsibilities, qualifications and training. In study responsibilities, identify every individual who will be involved in the consent process. Under qualifications, please include:

- Academic Title
- Institutional Affiliation (UCSF, ZSFG, SFVAHCS, etc.)
- Department
- Certifications

NOTE: This information is required and your application will be considered incomplete without it. If this study involves invasive or risky procedures, or procedures requiring special training or certification, please identify who will be conducting these procedures and provide details about their qualifications and training. Click the orange question mark for more information and examples.

Training Requirements:
The IRB requires that all Key Study Personnel complete Human Subjects Protection Training through **CITI** prior to approval of a new study, or a modification in which KSP are being added. More information on the CITI training requirement can be found on our **website.**

* **Definition of Key Study Personnel and CITI Training Requirements (Nov, 2015):** UCSF Key Study Personnel include the Principal Investigator, other investigators and research personnel who are directly involved in conducting research with study participants or who are directly involved in using study participants' identifiable private information during the course of the research. Key Personnel also include faculty mentors /advisors who provide direct oversight to Postdoctoral Fellows, Residents and Clinical Fellows serving as PI on the IRB application.

KSP Name	Description of Study Responsibilities - Briefly describe what will each person be doing on the study. If there are procedures requiring special expertise or certification, identify who will be carrying these out. Also identify who will be obtaining informed consent.	Qualifications, Licensure, and Training
Aguilera, Adrian, PhD	Site clinical trial lead /Peer training/Cultural adaptations	UC Berkeley Assistant Professor and UCSF clinical researcher with extensive research experience as well as clinical experience working with low-income and Spanish speaking populations.
Dr. Lyles, Courtney R PhD, PhD	Mixed methods and qualitative analyses	UCSF clinical researcher with extensive research experience as well as clinical experience working with low- income and Spanish speaking populations.
Schueller, Stephen M	Lead SilverCloud deployment, implementation	UC Irvine Associate professor with extensive research experience with

	evaluation	diverse populations.
Dr. Fortuna, Lisa R MD, MPH	Coordinate peer supporters/facilitate inreach	Chief of Psychiatry and Vice-Chair at Zuckerberg San Francisco General Hospital/UCSF.
Dr. Ochoa-Frongia, Lisa M MD	Recruit/Outreach via patient registry	Associate Professor of Medicine at UCSF, in the Division of General Internal Medicine at San Francisco General Hospital (SFGH). Practicing primary care physician and Associate Medical Director at Richard Fine People's Clinic.
Rosales, Karina	Assisting with day to day study operations including data collection, participant enrollment, follow up and obtaining informed consent.	UC Berkeley Research Assistant, UCSF affiliate, assisting Dr. Aguilera with day to day study operations including data collection, participant enrollment and follow up.

17.2 Affiliated Personnel:

Instructions:

This section is for personnel who are not listed in **Section 3.0: Grant Key Personnel Access to the Study** because their names were not found in the User Directory when both the iRIS Database and MyAccess directories were searched. Add any study personnel who fit ALL of the following criteria in the table below:

- They meet the definition of Key Study Personnel (see above), **and**
- They are associated with a UCSF-affiliated institution (e.g., SFVAHCS, Gladstone, Institute on Aging, Vitalant, NCIRE, SFDPH, or ZSFG), **and**
- They do not have a UCSF ID, **and**
- They do not need access to the study application and other study materials in iRIS.

Note: Attach a **CITI Certificate** for all persons listed below in the **Other Study Documents** section of the **Initial Review Submission Packet Form** after completing the **Study Application**.

Click the orange question mark icon to the right for more information on who to include and who not to include in this section.

Do not list personnel from outside sites/non-UCSF-affiliated institutions. Contacts for those sites (i.e. other institution, community-based site, foreign country, or Sovereign Native American nation) should be listed in the **Outside Sites** section of the application.

If there are no personnel on your study that meet the above criteria, leave this section blank.

Name	Institution	Telephone	E-mail	Role
No External Personnel has been added to this IRB Study				

Please describe the study responsibilities and qualifications of each affiliated person listed above:

18.0 End of Study Application

End of Study Application Form

To continue working on the Study Application:
Click on the section you need to edit in the left-hand menu. Remember to save through the entire Study Application after making changes.

If you are done working on the Study Application:
Important: Before proceeding, please go back to Section 4.0 Initial Screening Questions and **Save and Continue** through the form to make sure all the relevant sections and questions have been included. If you've changed any answers since you started, the branching may have changed. Your application will be incomplete and it will have to be returned for corrections.

Once you are sure the form is complete, click **Save and Continue**. If this is a new study, you will automatically enter the **Initial Review Submission Packet Form**, where you can attach **consent forms** or other **study documents**. Review the **Initial Review Submission Checklist** for a list of required attachments.

Answer all questions and attach all required documents to speed up your approval.

The UCSF IRB welcomes feedback about the IRB Study Application Form. Please click the link to answer a **survey** about the application form.

Statistical Design and Power

Preliminary Data Analysis

At the beginning of the project, Dr. Hoang will work with the research team, including the postdoctoral fellow overseeing quantitative data collection, to create data reporting tables. These data reporting tables will allow ongoing monitoring of demographic variables, to facilitate reporting to the DSM, and to support statistical analysis when data collection is completed. An example of a shell table is provided below.

We will screen the collected data using graphs and descriptive statistics to ensure data are within expected ranges, to check for outliers and abnormal values, and to ascertain variable distributions meet the assumptions of the statistical tests to be used. Using t-tests and chi-squared, we will test that random assignment was not compromised and that participants assigned to conditions are equivalent on important baseline demographics and outcome variables including age, gender, acculturation, technology literacy, and baseline depression (PHQ-9 and GAD-7). If any effects are found, we will adjust for them using the confounding variable as a covariate in model testing or as a stratification variable and will take the use of these statistical techniques into account in interpretation of the outcome. We will test to determine if there is differential attrition between conditions and will use the appropriate missing data strategies described in more detail below.

In all analyses using continuous predictors we will assess the linearity assumption by fitting higher-order polynomial terms and, for continuous outcomes, plotting residuals versus predictors. If the continuous predictor cannot be accommodated in simple form (e.g., linear and quadratic), it will be treated as categorical.

Summary of demographic and clinical characteristics of the study patients

Characteristics	**Peer-supported (N=)**	**Unsupported (N=)**	**P-value**
Demographics			
Age (mean, SD)			
Gender (%) Male Female			
Education			
Acculturation			
Technological literacy			
Previous use of mental health services			
Baseline clinical characteristics			
Depression PHQ-9 score (mean, SD)			
Anxiety GAD-7 score (mean, SD)			
Comorbidities			
Current use of antidepression medication			

Missing Data within Questionnaires

All self-report questionnaires will be administrated in Spanish via a secure web assessment platform (REDCap), which can immediately identify questions that have not been answered and prompt the participant to either answer the question or indicate that it was intentionally left blank. If missing data are identified, the study team will be alerted and will attempt to obtain the missing data from the participant. This includes providing a follow-up reminder via email and a follow-up phone call to determine if participants would rather answer assessments questions over the phone. These procedures minimize missing items and data. If a measure of scale is missing less than 20% of the data points that are needed to construct a scale, multiple imputation[107] will be used to infer the values based on the other elements of the scale that are not missing. If a scale or subscale is missing 20% or more of the data, that scale of subscale will be determined to be missing.

Missing Data Points

We note that based upon our previous work, we expect to obtain complete follow-up data on the majority of patients, including those discontinuing treatment.[72,73] Participants who drop out of treatment will be retained and we will continue to contact for assessment data, unless they withdraw consent. Completion of surveys will be promoted through the use of monetary incentives and consistent monitoring of study data. Participants who do not complete online assessments within a one-week window will be contacted by our research staff and provided the option to complete follow-up measures over the telephone. We do not expect the loss-to-follow up rates to differ across treatment arms. However, to be safe, in our analyses of longitudinal data we will build a logistic regression model for missing data, with the outcome being conditional missing data at a particular time point (conditional on participation up to that point) and will include possible predictors of missing data (i.e., gender, age, socio-economic factors, primary care clinic, etc). Loss-to-follow up rates at any point can then be calculated as the product of the conditional probabilities.[108] We will also conduct sensitivity analyses that consider any patients with missing data points as a separate group and see if missing data change the results (e.g., we will compare models of three groups of gender: male, female, and missing data).

Aim 1:

Quantitative:

Effectiveness: The primary outcome is the change in PHQ-9 and GAD-7 scores from baseline to 8-weeks (which this study is powered on). We will compare PHQ-9 and GAD-7 scores between the conditions using mixed-effect models adjusting for the intra-clinic correlation. Mixed-effect models generally require three time points, which is why we include a post-treatment assessment at 3-months. Although every effort will be made to avoid missing data (e.g., as described above e-mail/text/phone reminders for assessments, financial incentives for completing assessments), mixed-effect models are robust to missing data as they do not require complete case data (i.e., at every time point); thus, even participants with missing data at some assessments are included in the analysis and results are modeled on the basis of the available data. In the case of missing data, we will also analyze if missing data is related to any observable characteristics. Secondary clinical outcomes for this trial will consist of the PROMIS Social Health and clinical outcome data collected from the SilverCloud platform.

The mixed-effects models will analyze change in outcome variables and determine whether this change differs by condition (peer-supported vs. unsupported). Because randomization for the intervention will occur at the patient-level models will have patients nested by provider nested by clinic.

Use of Platform: A secondary outcome measure will be engagement with the SilverCloud platform as defined by total time on platform. *"Total time" on platform was chosen as the outcome measure rather than logins or other measures of frequency of engagement because differences in the length of each login may represent important differences in participant engagement.* Additionally, we will collect additional measures of use including (participants use each feature, number of peer coach interactions, and number of weeks that participants meet the expected use criteria of 3 logins per week).

All analyses will be conducted based on intention-to-treat principles. Additionally, we will include participant characteristics including sex, age, education, type of Latinx subgroup, acculturation, technology literacy, and previous use of mental health services as covariates. We will also explore baseline severity of symptoms of depression and anxiety as well as peer-supporter (e.g., to determine if certain peer supporters resulted in superior outcomes) as potential moderators of treatment response. The mixed-effect models will analyze whether patient outcomes across condition vary while including peer supporter along with other moderating factors.

Mediational analysis: We will also explore whether use of the platform mediates changes in clinical symptoms. Mediation will be examined using a bootstrapping procedure. This procedure produces bias-corrected and accelerated bootstrapped confidence intervals of the product of the direct pathways between condition and the mediator (a), the mediator and the outcome (b), and an estimate of the indirect effect (ab). To reduce potential bias resulting from multiple tests, mediation of use will be examined first using a composite of overall use of the intervention platform. A significant mediator of benefit, we will then proceed to examine frequency of different types of activities (e.g., time spent on platform, posting of content, reading of content, messages sent). We will compute different models for activity from users of the platform as well as by supporters of the platform.

Power analysis: The sample size was determined based on comparisons between intervention conditions (peer-supported vs. unsupported) regarding effectiveness. We used meta-analytic estimates of changes in depression and anxiety scores in digital interventions including both supported and unsupported dCBT. Conservatively, we estimated the sample size needed to detect a two-point difference in change on the PHQ-9 or GAD-7 between the peer-supported and unsupported arms. At an $\alpha = .05$ we would need 300 participants (150 per condition) to achieve power of 90%. Based on meta-analytic data, we estimate that attrition rates will be 25% in the supported arm and 29% in the peer-supported arm. Therefore, ***we increased our proposed sample size to adjust for estimated attrition resulting in estimates of 390 patient participants needed (195 per arm to maintain equivalent arms at baseline) to achieve excellent power on Aim 1.*** We indicate an example of this estimation using the PHQ-9 in the table below using the baseline values from the PHQ-9 value from our patient registry at ZSFG.

PHQ-9	Baseline	End	Pre-post	N	N + % attrition
Supported	15.1	8.1	-7.0	150	190 (25% attrition)
Unsupported	15.1	10.1	-5.0	150	195 (29% attrition)

Aim 2:

Quantitative: Guided by the RE-AIM framework, we will measure the impact on the primary care clinics including reach, adoption, and implementation. The primary outcome will be adoption. Adoption will be defined as the percent of providers with at least one enrolled patient with comparisons made across block of providers within each primary care clinics. We will also compare characteristics of providers with at least one enrolled patient on available data such as degree, specialty, and years practice. Reach will be defined as (a) the number of patients contacted via phone or brochure/text across the inreach and outreach arms and (b) the number of patients who create a login for SilverCloud, over the number of people determined to be eligible. Patient costs will include any time associated with engagement in treatment, including time spent on calls, messages, or on the dCBT site. Patient time in treatment will be captured through passive data collection estimating time on site and time of any phone calls that will be audiotaped. Self-reported salary will be used to estimate patient time cost. Peers will track time allocated to all support activities, including scheduling, messages, etc. Any scheduled phone sessions missed without 24-hour notice will be counted as having occurred as this is a cost incurred. dCBT costs will also include technical costs, including website maintenance and technical support. These costs will be calculated based on hourly rates for peers and payment made to SilverCloud for technical costs.

We will compare the proportion of patients referred, initiating, and completing treatment within each of the clinic blocks assigned to each implementation strategy using mixed-effects models using these outcomes represented as proportions as continuous outcome variables. These models will allow us to control for intraclinic clustering of providers as well as patient characteristics at each clinic (e.g., number of patients, percentage of Latinx patients). The two primary care clinics at ZSFG, consist of 166 FTE providers, 78 providers in the RFPC and 88 providers in the FHC. For randomization purposes we will create four blocks of providers (2 per clinic) consisting of approximately 40 providers each. Model comparisons will then compare blocks assigned to inreach vs. blocks assigned to outreach.

Aim 3: We will conduct a mixed-methods evaluation consisting of surveys, interviews, and focus groups.

Quantitative: For survey questions, we will use one-way ANOVAs to compare relative acceptability, appropriateness, and feasibility among the 2 treatment conditions. Any items that produce averages below the scale midpoint (3 = neither agree not disagree) will be addressed through analysis of the focus group and interview data to explore if we can determine aspects of the intervention or the patient or supporter experience that would correspond to those unfavorable ratings. We will compare peer-supported and unsupported using t-tests at each time point. We will also complete mediational analyses to determine if relational or technique factors mediate changes in depression.

Qualitative: We will conduct semi-structured interviews to ask patients and peers to assess attitudes towards the intervention, support component, cultural relevance and CBT mechanisms of use of cognitive and behavioral skills. We will also interview clinic leadership and providers to assess climate, clinic readiness, and attitudes towards the intervention.

For qualitative analysis we will use thematic analysis as described by Braun and Clarke.[98,99,103] This six-step analytical approach facilitates the process of becoming familiar with the data, systematically identifying individual codes, grouping those codes into preliminary themes,

defining and naming the final themes that commonly occurred across the entire data set, and then selecting examples from the data to accurately illustrate each theme. In thematic analysis, current theories or prior research can be used as initial categories as starting points for the data analysis. We will use Grol and Wensing's[104] multilevel model of barriers and facilitators as initial themes. These themes will include specific barriers and facilitators at the level of innovation, individual professional, patient, social context, organizational, and economic and political context. We will use a qualitative software analysis tool such as ATLAS.ti[105] to code the data. We will use guidelines for establishing reliability and validity in qualitative research which focus on ensuring the coherence, distinctness, and credibility of themes and subthemes.[106] We will use consensus to ensure that the analytic narrative represents the data, in relation to the research questions. In our consensus process, all reviewers will independently code all of the transcripts and meet to compare their coding to arrive at consensus judgments through open dialogue.[109-111] Consensus coding is designed to capture data complexity, avoid errors, reduce groupthink, and circumvent some research biases.