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Center for **Technology** and **Behavioral Health**

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Pontificia Universidad JAVERIANA Bogotá

Scaling Up Science-based Mental Health Interventions in Latin America

Implementation Research Project

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1.0 LIST OF ABBREVIATIONS

This section contains a comprehensive, alphabetical list of any abbreviations used throughout the protocol document.

AEs	Adverse Events
AUDIT	Alcohol Use Disorder Identification Test
BA	Behavioral Activation
BHIMC	Behavioral Health Integration in Medical Care
CFIR	Consolidated Framework for Implementation Research
CBT	Cognitive Behavioral Therapy
CRA	Community Reinforcement Approach to Behavioral Therapy
DALYs	Disability-Adjusted Life Years
DSMB	Data and Safety Monitoring Board
EPIS	Exploration, Preparation, Implementation and Sustainment Framework
GAD-7	Generalized Anxiety Disorder screener
GCP	Good Clinical Practice
IRB	Institutional Review Board
HPQ	Health and Work Performance Questionnaire
LMICs	Low and Middle Income Countries
mhGAP	Mental Health Gap Action Program
NIH	U.S. National Institutes of Health
NIMH	National Institute of Mental Health, U.S. National Institute of Health
NSMOS	Non-Study Medical and Other Services
PAHO	Pan American Health Organization
PHQ-9	Patient Health Questionnaire-9
PST	Problem Solving Therapy
QDS	Quick Drinking Screen
RE-AIM	Reach, Effectiveness, Adoption, Implementation, and Maintenance framework
SAEs	Serious Adverse Events
TDABC	Time-driven Activity-based Costing Approach
WHO	World Health Organization
WHODAS	World Health Organization Disability Assessment Schedule

2.0 PRÉCIS

2.1 Overall Study Objective

Conduct systematic, multi-site mental health implementation research in both rural and urban primary care settings with a broad group of stakeholders in the US and Latin America.

2.2 Study Intervention

We plan to launch and evaluate a new mental health service delivery model in Latin America. Specifically, in this new multi-component, mental health service delivery intervention, we propose to: (1) harness mobile behavioral health technology for mental health (with a primary focus on depression and a secondary focus on problematic alcohol and other substance abuse), (2) launch new workforce training and service delivery models (including the integration of technology into service delivery), (3) launch and evolve an integrated data management system for systematic data tracking and outcomes assessment, and (4) launch and grow a learning collaborative of organizations integrating mental health into primary care. We will launch this project at multiple primary care sites in various parts of Colombia, with a plan to inform subsequent adoption in several other Latin American countries, including Chile and Peru.

2.3 Study Design, Population, Outcomes, and Sample Size

We will initially pilot test this mental health service delivery model at a single primary care site and then refine the model based on pilot data. We will then expand implementation across 6 Colombia-based healthcare sites in urban and rural communities (including at least 1200 participants). Consistent with a modified stepped wedge design (multiple baseline design), we will implement the model across sites on a staggered basis and expand the number of sites in which we implement over time. By conducting this multi-site implementation research project, we can assess the extent to which the implementation model and associated outcomes are replicable across sites and/or the extent to which the model needs to be modified for differing contexts.

We will evaluate the ability of our proposed approach to accelerate the translation of evidence-based mental health services into practice and expand research capacity at multiple levels. Specifically, we will measure implementation outcomes, including: (1) the ability of this model to accelerate the adoption of science-based mental health service delivery (e.g., increase provision of evidence-based resources to more individuals), (2) the acceptability of the model for healthcare service delivery (the ability of the technology-based service-delivery model to increase patient activation and engagement in their own self-management), and (3) the cost-evaluation of services in the model. We will also collect patient level data outcomes as a secondary focus to assess (4) the model's impact on public/population health (e.g., its effects on accelerating improved behavioral health and health outcomes, and improving patient quality of life, functioning, etc.).

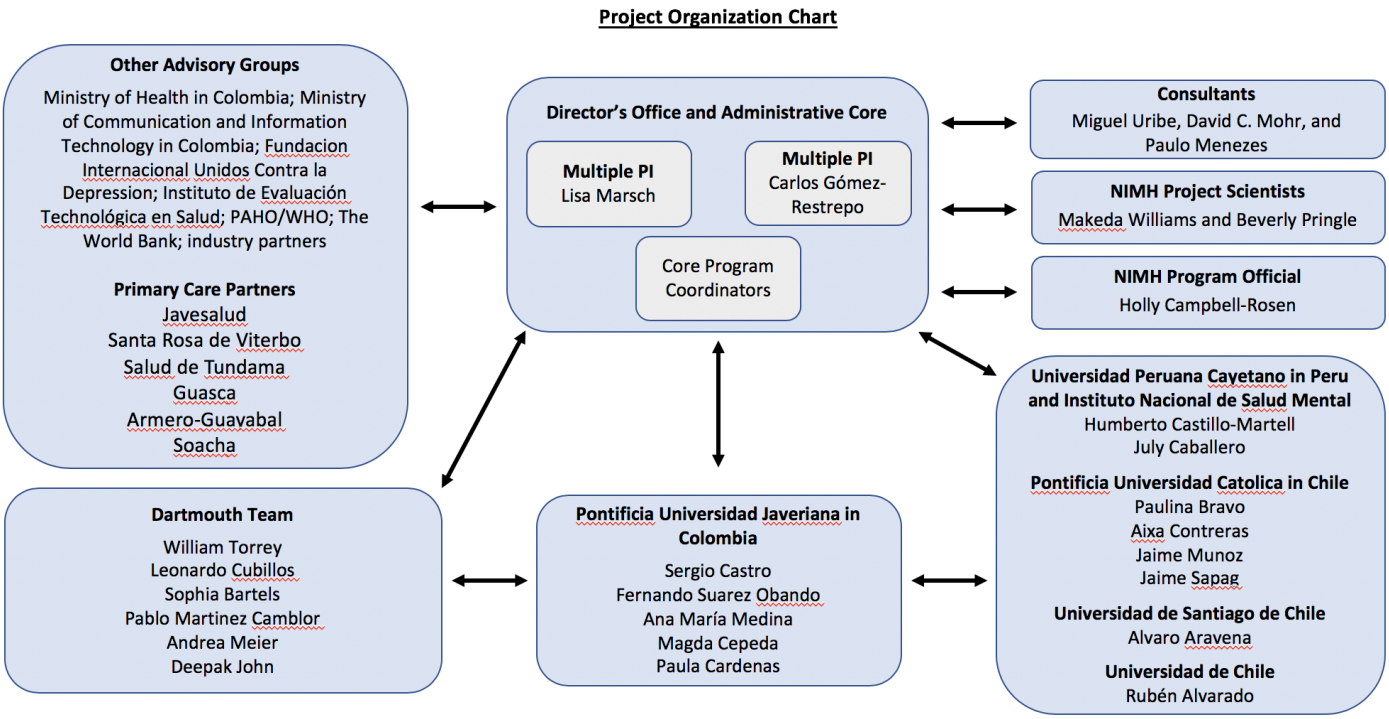
We will also use implementation context measures to evaluate barriers and facilitators to implementation in each of the following domains: intervention characteristics, organization characteristics (e.g., climate, readiness), individual characteristics (i.e., provider/staff attitudes, experiences; patient attitudes and experiences), and external influences (e.g., socio-political characteristics local technology infrastructure i.e., wireless in the community, state policy/regulations, and reimbursement models). Strategies related to planning, facilitating provider and patient engagement in use of the novel mental health service delivery model, and potential sustainability issues

will also be explored. We will additionally conduct exploratory moderator/mediator analyses to examine how implementation context variables relate to implementation outcomes.

2.4 Potential Impact

Overall, this project will create new knowledge to inform unprecedented, science-based approaches to scaling-up mental health implementation research and building sustainable research capacity and science-based policies and programs in Latin America. This project brings together an outstanding expert team to test and refine an entirely new model for delivering widespread, science-based, mental health care in Latin America. This project may also serve as an important demonstration project to low resource settings globally as they tackle the significant burden of mental health disorders and scale-up access to evidence-based models of mental health service delivery.

3.0 PROJECT ORGANIZATION, ROLES AND RESPONSIBILITIES



As illustrated in the **Organizational chart,** the **Project Director's Office** will provide overall leadership for the project. The **Multiple Principal Investigators** [PIs] (Lisa A Marsch, PhD and Carlos Gómez Restrepo, MD) will constitute the Project Director's Office. In their role in the Director's Office, the Multiple PIs will collaborate to integrate efforts across sites, project collaborators, and project activities. The PIs will be responsible for ensuring all project Aims are successfully realized. Dr. Marsch will serve as Contact PI and will be responsible for ensuring all NIMH, IRB and other reporting requirements are successfully met. Dr. Marsch will also be primarily responsible for overseeing all proposed activities to be conducted out of Dartmouth College (e.g., data analyses; supervision of data collection; supervision of implementation of novel mental health service delivery model), while Dr. Gómez Restrepo will be responsible for overseeing all proposed activities to be conducted out of Pontificia Universidad Javeriana in Colombia (oversight of all local research staff and

local implementation research and capacity building activities). The Multiple PIs will also coordinate project activities with NIMH staff and will coordinate the engagement of the Consultants throughout the life of the project. The Director's Office will also assume primary responsibility for facilitating activities designed to synthesize research findings and promote joint publications and presentations among project Investigators. The Office will also work to resolve any potential disputes/concerns that may arise.

Consultants and Investigators. The Director's Office will be advised by a team of expert consultants (Miguel Uribe, MD; David C. Mohr, PhD, Paulo Rossi Menezes, MD). As detailed in his biographical sketch, Dr. Uribe (in partnership with Gómez Restrepo) has conducted extensive work on integrating depression care into primary care in Colombia and currently serves as an advisor to the World Bank in Washington, DC. We have further engaged both US and Latin American-based research teams conducting implementation research that employs mobile health technology in several regions of Latin America (Dr. David Mohr at Northwestern University in Chicago and Dr. Paulo Rossi Menezes at the University of São Paulo in Brazil). This partnership will leverage the investment of NIMH in these collective activities to enable a new level of discovery and accomplishment across projects and offer the opportunity to accelerate the tempo and scientific achievement from this line of research.

The Director's Office will also be advised by members of the investigative team at both Dartmouth and Pontificia Universidad Javeriana. At Dartmouth, this includes William Torrey, MD a psychiatrist with extensive experience using innovative models for integrating mental health care into primary care; Pablo Martinez, PhD, a statistician at the Dartmouth Institute of Health Policy and Clinical Practice; and Leonardo Cubillos, MD, a psychiatrist formerly working at the World Bank in Washington DC in the areas of poverty and mental health in Latin America (Colombia is his birthplace) and now a psychiatrist with our group at Dartmouth. Andrea Meier serves as a trainer/monitor of several assessment activities.

At Pontificia Universidad Javeriana, Dr. Sergio Castro (a psychiatrist), Dr. Fernando Suarez Obando (a PhD student under Dr. Gómez Restrepo), Dr. Ana María Medina (an anthropologist), and Dr. Magda Cepeda (a doctor with a PhD in epidemiology) will serve as Co-Investigators and project directors overseeing research staff activity in the implementation trial (under the leadership of Dr. Gómez Restrepo).

Governmental, Non-Governmental and Multilateral Organizations. The Director's Office will also be advised by a broad array of stakeholders including academic organizations (Dartmouth College in the US; Pontificia Universidad Javeriana in Colombia; Universidad Peruana Cayetano in Peru; Pontificia Universidad Catolica in Chile), governmental organizations (Ministry of Health in Colombia; National Institute of Mental Health in Peru), as well as non-governmental and/or multilateral organizations (PAHO/WHO; The World Bank; industry partners; and primary care and regional hospital systems in Latin America).

We will also include perspectives of a non-profit patient advocacy organization ("Fundacion Internacional Unidos Contra la Depresión" – The International Foundation United Against Depression) and a public/private non-profit organization focused on quality decision-making in clinical practice and health policy ("Instituto de Evaluación Technológica en Salud" – The Institute of Technical Evaluation in Health). We had additionally engaged several large insurance companies in Colombia, which will

be key to the sustainability of this work.

Overall, we have been fortunate to assemble an outstanding and broad team of collaborators and stakeholders which greatly enhances our ability to achieve the goals of the proposed project. These partnerships will also ensure that the study design is responsive to local needs, resources and expertise and enables synergies beyond what can be achieved through a traditional research study.

Advisors from Chile and Peru. Although implementation activities will primarily take place in Colombia, experts from the countries of Chile and Peru will participate as collaborators throughout the entire project as part of research capacity-building activities (to inform implementation and shared learning in other parts of Latin America).

National Institute of Mental Health (NIMH) Project Scientists. As per the Cooperative Agreement, the project team will work closely in partnership with NIMH Project Scientists on the execution of the proposed work and the evolution/refinement of this work over time based on NIH input, learning based on data collected over time, and shared learning among grantees under this funding opportunity (Drs. Denise Pintello and Beverly Pringle). We will also work closely with NIMH Program Official Dr. Holly Campbell-Rosen.

Administrative Staff within the Core. Program coordinator administrative support staff will work under the leadership of the Director's Office to support the Administrative Core. One part-time support staff will work at Dartmouth under the guidance of Dr. Marsch and the other will work at Pontificia Universidad Javeriana in Colombia under the guidance of Dr. Carlos Gómez Restrepo. These individuals will coordinate logistics for all in-person and webinar meetings, arrange space needs, oversee the timeline, organize all project publications and presentations, IRB approval and budget on project activities.

4.0 INTRODUCTION

4.1 Background and Significance to the Field

Mental health disorders are increasingly recognized as a major cause of the global burden of disease, accounting for an estimated 7.4% of the disease burden worldwide[1] and significantly contributing to disability and death. The overall annual economic cost for mental health disorders is estimated at over $300 billion and is expected to exceed $16 trillion over the next 20 years.[2, 3] Expanding access to mental health care in a manner that can rapidly scale and have a substantial population impact is a significant challenge globally.[4]

This challenge is particularly evident in low and middle-income countries (LMICs) where more than half of the world's population live.[5-7] Between 76-85% of persons with severe mental disorders in LMICs receive no treatment at all for these problems. The healthcare workforce in LMICs is also grossly insufficient – with an average of one psychiatrist to serve every 200,000 people and even fewer mental health providers trained in the delivery of psychosocial interventions. Additionally, only 36% of persons in LMICs are covered by mental health legislation, in stark contrast to 92% of persons in high-income countries.

Latin America is one region of the world composed of LMICs where the burden of mental health problems is high and services for mental health are low (and account for <2% of the health budget in

the region).[8] Over 37%, 59% and 71% of persons in Latin America with severe mental illness, major depression, and alcohol use disorders, respectively, are in need of treatment but do not receive care.[9] In the Latin American country of Colombia, non-communicable diseases account for over 61% of total disability-adjusted life years (DALYs), with mental health disorders accounting for almost 13% of those DALYs. A recent National Mental Health Survey in Colombia, conducted in 2003,[10] showed that 8 out of 20 Colombians has a lifetime prevalence of one or more mental health disorders. Depression and substance use, often coupled with other mental health problems resulting from endemic violence in Colombia, are particularly striking concerns in the region. Only 11%[10] of persons with a mental health disorder in Colombia receive mental health care.

In 2008, the World Health Organization (WHO) launched the Mental Health Gap Action Program (mhGAP) including strategies and activities to scale up care for mental, neurological, and substance abuse disorders – with a priority focus on LMICs.[11] Recognizing the high burden of disease from mental disorders in the Latin American region and the close relationship between mental health and physical health, the Directing Council of the Pan American Health Organization (PAHO) within the WHO adopted a Plan of Action on Mental Health in its Strategic Plan 2014-2019.[12] The Strategy and Plan of Action calls for Member States to position mental health as a priority and lays the route to improve mental health programs in the region over the next 10 years.

Colombia has embraced this plan and is currently preparing to launch (under the leadership of the Colombian Ministry of Health) a new model of mental health care (called "Modelo Integral en Atención en Salud" – Integrated Model of Health Care)[13] that will reinforce primary care-based mental health care – a long-standing weakness in the Colombian health system. The articulated goals of the model are to ensure access to care, continuity of care, integration of care, capacity to resolve health problems and quality of care. Ongoing measurement of patient outcomes is another priority within the model.

In order to achieve the goals of the model, a key element is to leverage empirically-supported mobile behavioral health technology to create an entirely new model of mental health service delivery within primary care. Indeed PAHO noted the need to "study and maximize use of technology (mobile phones…and Internet) to guarantee access to mental health services in remote and neglected communities."[12] Specifically, advances in digital technologies have created unprecedented opportunities to assess and modify behavioral health at a population level and thus facilitate the rapid and widespread "scaling-up" of evidence-based mental health care. Over 90% of persons worldwide have access to mobile phone services, with Colombians having an average of 108.3 phones for every 100 inhabitants (an average of more than one phone per person). Growing evidence suggests that increased access to these technologies is also evident in many traditionally underserved populations where disparities are prevalent.

Another key element of Colombia's mental health care model is human resource development focused on the creation of mental health skills within primary care teams. Given the strikingly limited availability of mental health trained workforce in Colombia and elsewhere in Latin America (as reviewed above), raising awareness of evidence-based screening and interventions for mental health within the primary care workforce is critical to integrated care.

Similar models of mental health care are in various stages of planning in other Latin American countries, including Chile and Peru.[14-16]

The proposed project was developed in response to the striking mental health treatment service delivery needs in Latin America broadly (and Colombia in particular) and the strong commitment to making substantive changes in the region.

As detailed in this protocol, we will (1) harness mobile behavioral health technology for mental health (with a primary focus on depression and a secondary focus on problematic alcohol use) (2) launch new workforce training and service delivery models (including the integration of technology into service delivery), (3) launch and evolve an integrated data management system for systematic data tracking and outcomes assessment, and (4) launch and grow a learning collaborative of organizations integrating mental health into primary care. We will launch this project at multiple primary care sites in various parts of Colombia, with a plan to inform potential subsequent adoption in several other Latin American countries, including Chile and Peru.

5.0 OBJECTIVES

5.1 Primary Objectives

Administrative Core
Support a core organizational structure and management approach to maximally benefit from a broad array of stakeholders and ensure efficient and successful coordination and integration of the activities across project Cores

Aim1a: To provide scientific and programmatic leadership to ensure efficient and successful coordination and integration of the activities across the Hub's projects.

Aim 1b: To provide a novel infrastructure to enhance synergy among an interdisciplinary expert team by facilitating productive communication, centralization of knowledge and resources, and integration of methods and results across research activities

Scale-Up Core
Aim 2. Conduct systematic, multi-site mental health implementation research in both rural and urban primary care settings with a broad group of stakeholders in the US and Latin America

Capacity Building Core
Use science-based methods and information to build sustainable capacity for conducting mental health implementation research and informing mental health policies and programs in Latin America

Aim 3a: Establish resources and an infrastructure to aid Colombia and its regional partners of Chile and Peru to build capacity for mental health implementation research

Aim 3b: Build sustainable capacity to use science-based methods and information for developing mental health policies and programs

5.2 Secondary Objective(s)

A secondary Aim of this project is to engage in ongoing dialogue and shared learning activities with other "hubs" of grantees funded under this same NIMH funding mechanism, focused on scaling up evidence-based mental health care in low and middle-income countries.

This project protocol focuses primarily on the planned human subjects activity within the Scale-Up Core (multi-site mental health implementation research project).

6.0 FORMATIVE RESEARCH

In preparation for the Scale-Up Core's multi-site implementation research project, our team has engaged in an array of formative research activities. These activities are briefly described in this section. These activities launched after a leadership planning team held at Dartmouth College in June 2016, followed by our all-team project kick-off meeting and initial industry advisory board meeting in Bogotá, Colombia in September 2016. All formative research activities were reviewed and appropriately approved by the Institutional Review Boards at Dartmouth College as well as Pontificia Universidad Javeriana (and study sites, as needed). These preparatory activities were deemed exempt from review by the NIMH Data and Safety Monitoring Board (DSMB).

These formative research activities included:

Technology Usage/Access Survey in Colombia

Focus Groups and In-Depth Interviews with Multiple Stakeholders

Behavioral Health Integration in Medical Care (BHIMC) assessment: Adapation for Colombia and baseline assessment at primary care study sites

We will discuss each of these activities, in turn.

6.1. Technology Usage/Access Survey in Colombia

We conducted an anonymous survey in Colombia to examine the extent to which patients in primary care systems use Internet, mobile devices, such as smartphones (e.g., iPhone, Android, Blackberry) and tablet computers (e.g., iPad), to answer clinical questions and find medical and health information.

The specific objectives of this project were to:

- Evaluate socioeconomic characteristics of patients and their possible relation to patterns of technology use
- Establish health care service conditions of patients in the primary care network
- Assess patient's mobile device use for finding medical information related to general health and mental health

Methods
Survey sites

We recruited participants to complete the survey from 6 sites. Specifically, we recruited participants in Bogotá D.C. at 1) Fundación Javeriana de Servicios Médicos ondontológicos inter-universitarios "Carlos Márquez Villegas" Javesalud (The Javeriana Foundation of Inter-University Odontologic Medical Services). We also recruited participants in two health care systems in the town of Duitama (Boyacá): 2) Empresa Social del Estado Hospital Regional de Duitama (The State Social Services Regional Hospital Of Duitama) and 3) Santa Rosa de Viterbo Regional Health Center. And, we recruited participants in three healthcare systems in Tolima: 4) Hospital Armero-Guayabal, 5) Hospital de Chaparral, and 6) Hospital Granja de Lérida, Primer Nivel. These regions span both urban and rural (e.g., farming) communities and thus enable broader generalizability of survey results.

Our research team at Javieriana University has academic partnerships between the Javeriana University and Javesalud, Hospital Regional de Duitama and Santa Rosa. Via this project, the research team at Javeriana has established partners with Lerida, Chaparral, and Guayabal. Javesalud is in Bogatá, 30 minutes from Javeriana. Duitama and Santa Rosa are both about 3 hours from Bogotá, and Javeriana has interns from the School of Medicine in each of these locations and the Director of the interns in Duitama is part of our research project as a Psychiatrist in Lerida.

Survey design and implementation
The survey explored facilitators of mobile device use in medical information seeking, barriers to access, internet connection conditions, familiarity with medical resources, and most frequently used resources. The questions in the survey were designed by the research team members, based on prior similar survey studies (such as technology assessments conducted in local hospitals and/or low and middle income countries, as well as the Colombian mental health survey).

The survey was implemented via a computerized survey engine (LimeSurvey) delivered on a tablet to patients recruited in waiting rooms of the participating primary care survey sites. At each site, a research assistant asked patients if they would be willing to complete the survey during their time in the waiting room before their medical appointment. The research assistant explained the nature of the survey and was available to supervise the process and answer any questions from patients, as needed. The survey was self-administered and anonymous and generally took about 10-15 minutes to complete.

As of the time of submission of this protocol for review by the NIMH Data and Safety Monitoring Board (DSMB), we have completed participant recruitment for this survey and have a total of 1,580 completed surveys from patients across our survey sites. These data have been helpful in planning our implementation project across sites. For example, these data have been helpful in understanding the likelihood that patients can access mobile therapeutic tools for mental health on smartphones (as opposed to other sources, such as computers set-up onsite at primary care sites) as well as patients' interest in using digital therapeutic tools for mental health. Based on data collected to date, we expect that more patients in Javesalud will have access to smartphones compared to patients in more rural settings (where access to the mobile intervention may include computer access at primary care sites).

6.2. Focus Groups and In-Depth Interviews with Multiple Stakeholders

Objective

We conducted qualitative research to explore perceptions, abilities, attitudes, practices and experiences of health professionals, administrators, patients and community organizations on access, continuity, integration, quality and resolution of problems in mental health in primary care. This research was intended to understand existing models of providing screening and mental health care to patients in Colombia. As part of this research, participants were asked to discuss the possible use of mobile health technologies for assessment and follow-up support in the treatment of depression and alcohol use disorders.

Methods

We primarily used a focus group methodology with four different groups of participants (as detailed below). In addition, we performed semi-structured in-depth interviews to deepen our understanding of important aspects identified in the focus groups.

Survey sites

We recruited participants for this qualitative research from the same 6 sites where we conducted the technology survey described above (to enable broad sampling and increase generalizability): 1) Fundación Javeriana de Servicios Médicos ondontológicos inter-universitarios "Carlos Márquez Villegas" Javesalud (The Javeriana Foundation of Inter-University Odontologic Medical Services). 2) Empresa Social del Estado Hospital Regional de Duitama (The State Social Services Regional Hospital Of Duitama) and 3) Santa Rosa de Viterbo Hospital in Duitama (Boyacá). And, we recruited participants in three healthcare systems in Tolima: 4) Hospital Armero-Guayabal, 5) Hospital de Chaparral, and 6) Hospital Granja de Lérida, Primer Nivel.

Participants

We identified the following groups of participants for the focus groups and in-depth interviews in order to obtain diverse stakeholder input:

- **Health professionals** (nurses, physicians, psychologists and social workers) were asked about the importance of identifying and treating mental health problems (particularly depression and alcohol), knowledge they have about the clinical guidelines in Colombia for treatment of depression and alcohol use disorders, the possibility and acceptability of working with patients with depression or alcohol use disorders, their interest in encouraging patients' active involvement in their own care, among other fundamental aspects to improve the quality and integration in health care and expected benefits or burden for their practice (time, etc.) if depression and alcohol is addressed in a systematic way.

- **Administrative workers** (e.g., intake staff, practice managers, administrative coordinators, technology directors, billing administrators) were asked about technical and administrative possibilities of introducing new elements into the care model, such as, mobile applications and other information technology solutions in healthcare, forms of financing, coordination with national structures such as the Ministry of information and communications technologies to link patient data to health insurance providers' information platforms. Similarly, we inquired about what changes may be needed in workflows to improve mental health care.

- **Patients** were asked about the facilitators and barriers to accessing health services and particularly mental health services in primary care, quality and timeliness of care, facilities for obtaining specialized mental health care, and proactivity of patients in treatment.

- **Community organizations** (e.g., patient associations) represented an important participant group because they may become support networks for patients with depression and alcohol use disorders. They were asked about their facilitators and barriers for behavioral health promotion, and referral to health services and particularly to mental health services in primary care, quality and timeliness of care.

Focus Groups Procedure
We held focus groups with each group of participants in all study sites in Colombia (as described above) to achieve a total of 14 focus groups (with 104 participants). Each focus group convened between 6 to 10 people. In Bogotá, we held two additional focus groups, one with patients diagnosed with major depression and the other with patients diagnosed with an alcohol use disorder due to the availability of patients' groups.

Focus groups were led by an experienced facilitator (anthropologist) who received training in focus group methodology and the specific topics to discuss with the group. The groups also had two additional members of the research team present to observe, and take notes during the focus group. Each focus group was audio recorded for analysis. Each focus group lasted about 1.5 to 2 hours and each group's meeting was held in private meeting rooms.

In-Depth Interviews
We conducted 9 semi-structured interviews to enable a more in-depth understanding of the elements identified in the focus groups, including 3 patients with depression and/or alcohol use disorder, 3 health professionals, and 3 administrative workers. Note that community members were not included in in-depth interviews because they were not part of the health care system (as were the other three stakeholder groups). Participants were recruited from focus groups by convenience, availability and willingness to participate. Each interview lasted approximately 60 minutes. Interviews were conducted by 2 interviewers with training in qualitative methods and experience in conducting research in health topics (the same staff who conducted focus groups). Participants provided permission to digitally record the interview and, in addition, notes were taken by the interviewer.

These qualitative data from focus groups and in-depth interviews informed our planned model of mental health screening and care that we plan to implement in our upcoming implementation research project. These data are still being collected but we expect they will inform our model of implementation into the workflow at each study site and increase our understanding of other mental health resources (if any) available in the communities surrounding our study sites.

6.3. Behavioral Health Integration in Medical Care (BHIMC) assessment: Adaptation for Latin America and baseline assessment at primary care study sites

Objective
One of the aims of this research project is to assess the organizational capacity of a sample of Colombian primary health service centers to address behavioral health conditions. To accomplish this, we systematically modified the Behavioral Health Integration in Medical Care (BHIMC) measure (which has been validated in the U.S.) for use in the Colombian health care system. We then completed this modified BHIMC measure as a baseline assessment to characterize the extent to which the primary care sites that will participate in the implementation trial have embraced screening/behavioral health in their service delivery model. As described in Section 12.0 below, we also plan to administer this tool at these

study sites over time during the implementation research project to capture change over time (pre/post implementation of the novel mental health care model).

The Measure

The Behavioral Health Integration in Medical Care (BHIMC) index is an organizational measure of the level of behavioral health integration in medical practice settings. It evaluates policy, clinical practice and workforce dimensions of integration using mixed methods, i.e. combination of document review and observation. The structure of the half day site visit is as follows: (1) Meet with leadership (Chief Executive Officer, Chief Medical Officer, Chief of Operations, Directors of Behavioral Health and Nursing, etc.), (2) Tour the organization, (3) Interview with providers (3-5 in small group), (4) Interview with support staff (3-5 in small group), (5) Interview with patients (individually), (6) Review documents (4-5 patient records, manuals, brochures, informational material, screening and intake forms, etc.), and (7) Debrief.

Data from these sources are used to make ratings on a 36-item 5-point rating scale: 1 = Minimally Integrated (MI); 2= Minimally Integrated/Partially Integrated (MI/PI); 3 = Partially Integrated (PI); 4= Partially Integrated/Fully Integrated (PI/FI); 5 = Fully Integrated (FI). As reflected in this scale, scores of 2 or 4 are reflective of intermediary levels between the standards established by scores of 1 (MI), 3 (PI) and 5 (FI). The BHIMC has been used in other contexts (by the Dartmouth team) to assess behavioral health integration in primary care, and community health clinics.[17] It was originally developed with the support of the U.S. Substance Abuse and Mental Health Services Administration (SAMHSA).

Adaptation of BHIMC for use in Colombia

To adapt the BHIMC, we divided our work into four concurrent tasks:

a. Understand the evidence of **value of integration** of mental health in primary health services in low and middle income countries

   [Note that we are separately conducting a systematic review on this topic and we registered this protocol in the Prospero Database on March 1, 2017 https://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42017057340].

b. Understand the **BHIMC** (the original instrument developed and used in the USA)

c. Based on the two above, slightly **adapt** the existing tools and processes to the Colombian context. This largely included translation to Spanish and changing reference to payer systems in the Colombian (and not the U.S.) context.

d. Work jointly with **the industry actors** (health insurance payers via our industry advisory board) to ensure that the adaptation is grounded in the existing reality

Briefly, in understanding the BHIMC, the core team read and analyzed the associated manual about this instrument, met with the original Dartmouth-based developer of the instrument, and held multiple rounds of discussion to adapt several questions and the gradients of the scale to the Colombian health care system. The core team also redesigned the process based on the local norms and values. In so

doing, the team periodically consulted with various members of our industry advisory board in Colombia to ensure the tool best reflects the reality of the Colombian context.

Note that we conducted a systematic search for any similar instruments that had been used in Colombia but did not find any (and thus decided to adapt the BHIMC to the Colombian health care context).

The core team then participated in a 3-day, face to face training (held at Pontificia Universidad Javeriana in Bogotá) on the use of the BHIMC, led by a team member from Dartmouth who has long-standing expertise in the use of the BHIMC (Andrea Meier at the Dartmouth Center for Technology and Behavioral Health, directed by Dr. Marsch). Given the interest in the use of this tool in Colombia, various members of the Colombian Ministry of Health also participated in this training. On day 1 of the training, the Core team met to review the logistics of the training and then Ms. Meier led a presentation on the background of the BHIMC measure, scoring sheets and associated reports. She also provided a practicum using sample documents and case studies. On day 2 of the training, the team conducted a field visit and assessment with the BHIMC at a health care site that agreed to serve as a training site (to help ensure the real-world training experience for trainees). During this field visit, the core team piloted the adapted tool and process. On day 3 of the training, the trainees completed BHIMC scoring (including associated graphs and summaries) based on the prior day's field site visit.

We have completed baseline BHIMC data collection at the primary care sites that will collaborate on our planned implementation research project. And as noted elsewhere, we plan to administer this tool at these study sites over time (every year) during the implementation research project to capture change over time (pre/post implementation of the novel mental health care model).

7.0 STUDY DESIGN

7.1 Summary Overview of Implementation Study Design

In the proposed implementation research project, we plan to launch and evaluate a new mental health service delivery model in Latin America. Specifically, in this new mental health service delivery model, we propose to: (1) harness mobile behavioral health technology for mental health (with a primary focus on depression and a secondary focus on problematic alcohol use), (2) launch new workforce training and service delivery models (including the integration of technology into service delivery), (3) launch and evolve an integrated data management system for systematic data tracking and outcomes assessment, and (4) launch and grow a learning collaborative of organizations integrating mental health into primary care. We will launch this project at multiple primary care sites in various parts of Colombia, with a plan to inform subsequent adoption in several other Latin American countries, including Chile and Peru.

As detailed below, we will initially pilot test this service delivery model at a single site (starting in the late summer of 2017, which is year 2 of the project) and then refine the model based on pilot data. We will then expand implementation across multiple Colombia-based healthcare sites in urban and rural communities on a staggered basis (Years Two-Five). Consistent with a modified stepped wedge design (multiple baseline design),[18, 19] we will implement across sites on a staggered basis and expand the number of sites in which we implement over time. By conducting this multi-site implementation research project, we can assess the extent to which the implementation model and associated outcomes are replicable across sites and/or the extent to which the model needs to be modified for differing

contexts.

We will evaluate (Years Two-Five) the ability of our proposed approach to accelerate the translation of evidence-based mental health services into practice and expand research capacity at multiple levels. Specifically, we will measure implementation outcomes, including: (1) the ability of this model to accelerate the adoption of science-based mental health service delivery (e.g., increase provision of evidence-based resources to more individuals), (2) the acceptability of the model for healthcare service delivery (the ability of the technology-based service-delivery model to increase patient activation and engagement in their own self-management), and (3) the cost-evaluation of services in the model. We will also collect patient level data outcomes (depression, quality of life, alcohol use) as a secondary focus to assess (4) the model's impact on public/population health (e.g., its effects on accelerating improved behavioral health and health outcomes, and improving patient quality of life, functioning, etc.). Patient level data will be collected via computerized assessment and will be deidentified (not linked to patient name, date of birth or other identifying information).

We will also measure implementation context factors to evaluate barriers and facilitators to implementation in each of the following domains: intervention characteristics, organization characteristics (e.g., climate, readiness), individual characteristics (i.e., provider/staff attitudes, experiences; patient attitudes and experiences), and external influences (e.g., socio-political characteristics local technology infrastructure i.e., wireless in the community, state policy/regulations, and reimbursement models). Strategies related to planning, facilitating provider and patient engagement in use of the novel mental health service delivery model, and potential sustainability issues will also be explored. We will additionally conduct exploratory moderator/mediator analyses to examine how implementation context variables relate to implementation outcomes.

We will first describe in more detail the various components of the mental health care model to be implemented followed by a detailed description of the proposed implementation research project protocol and all planned assessments.

8.0 COMPONENTS OF MENTAL HEALTH CARE MODEL TO BE IMPLEMENTED

In this section, we first describe each aspect of the mental health service delivery model, followed by our implementation research plan.

(1) Mobile behavioral health technologies for mental health. *As reviewed above* -- given the ubiquity of access to technology worldwide -- patient monitoring and behavior change tools delivered on mobile platforms may enable widespread reach and scalability of evidence-based mental health interventions. A growing body of scientific research has shown that mobile behavioral health tools can have a large impact on health behavior and health outcomes, and increase quality, reach, and personalization of care in a manner that is cost-effective. Mobile behavioral health tools can produce health outcomes that are comparable to, or better than, outcomes produced by care delivered by highly trained clinicians. Also, by having on-demand access to "just in time" therapeutic support via electronic devices, individuals can prevent costly escalation of problems related to behavioral health and unnecessary healthcare utilization.[20-28] Technology provides new opportunities for self-care in response to the needs of each individual.

Technology-based interventions can be available 24/7 and thus allow for "on-demand," ubiquitous

access to therapeutic support, thereby creating unprecedented models of intervention delivery and reducing barriers to accessing care. This provides the possibility of addressing the "5,000 hour problem" -- namely that patients typically only spend a few hours a year in front of a doctor and in the 5,000+ other waking hours, their doctor neither knows what they are doing nor has effective tools to support them in the management of their health care.[29] Leveraging technology in this way offers great promise for leading to new models for science-based approaches for promoting behavioral health and health outcomes.[30-33]

Mobile behavioral health technology represents a key part of our planned mental health service delivery model for scaling-up access to evidence-based mental health care in Latin America. A key component of this system is a novel, mobile-based platform (Laddr® from Square2 Systems) that offers science-based self-regulation monitoring and health behavior change tools via an integrated platform to a wide array of populations. Laddr embraces the commonalities in the principles of effective behavior change and transcends the currently siloed nature of mobile health tools. This includes tools for activating behavior change, solving problems and overcoming obstacles to effective behavior change, teaching skills and providing guidance on the execution of behavior change, and maintaining the end user's motivation to change. Laddr enables frequent, longitudinal assessment of patient-reported outcomes in naturalistic contexts, offers science-based self-regulation behavior change tools of relevance to an array of populations, and enables ongoing monitoring of health behavior. The uniqueness of Laddr lies in the fact that it integrates tools that have been developed via an iterative patient-centered approach and shown (in over a dozen NIH-supported studies conducted by Multiple Principal Investigator Dr. Marsch and colleagues) to be highly effective for a wide array of behavioral phenomena ranging from, for example, substance misuse, alcohol misuse, mental health, risk-taking, chronic pain management, medication adherence, diet, exercise, diabetes management, and smoking.[20-28] Laddr is available on multiple platforms (including desktop, Android, iPad, and tablets). To our knowledge, this is the only mobile ecosystem that employs the fundamental principles behind the science of behavior change to flexibly apply to a broad array of populations based on their goals, needs, and preferences and independent of their "disease" or "disorder".

Laddr will be offered to focus primarily on depression management – the most significant mental health problem experienced in Latin America. Specifically, the core functionality of Laddr (e.g., problem-solving therapy) will be structured to focus on an end user's management of depression and its impact on their functioning and quality of life. The program will secondarily focus on problematic alcohol use and its relationship to depression management.

Consistent with the science of behavior change described above, these key strategies targeting depression management (and secondarily alcohol abuse and its relation to depression) focus on increasing an individual's personal and social resources that support and reinforce healthy, goal-directed behavior and reduce self-defeating behavior, including tools and resources to:

1. Help activate/motivate behavior change based on an individual's values (a scientific process known as **"Behavioral Activation" [BA]**). In this process, individuals are provided with tools and strategies to help identify their values, in areas such as health, parenting, family relations, social relations, work/career, leisure, and/or personal growth. BA helps individuals take steps to create an environment that supports healthy and goal-directed behavior consistent with their values. It also includes systematic tracking of behavior and consequences of behavior to help identify and disrupt (with learned skills) self-defeating behavioral patterns. For example, this may include disrupting negative thought-patterns by identifying and understanding triggers of

negative thought-patterns and self-defeating responses to such triggers and then replacing self-defeating responses to triggers with alternative, coping strategies.

2. Effectively solve problems needed for successful behavior change (a scientific process known as "**Problem Solving Therapy" [PST]**).[34-36] PST is a practical and easily learned intervention for many self-defeating behaviors, including depression. The goal of PST is to teach individuals skills in solving problems as a means of enabling them to self-manage and to control negative states and behavior. Its treatment process focuses on participants' appraisal of specific problems, their identification of the best possible solutions, and the practical implementation of those solutions, as well as increasing exposure to pleasant[37, 38] events.

3. Teach skills and provide guidance in the execution of behavior change (scientific processes known as "**Cognitive Behavioral Therapy**" **[CBT]**[39, 40] and the "**Community Reinforcement Approach" [CRA]**[41] to behavior change). CBT teaches a broad array of skills and behaviors to manage problematic emotions, behaviors, and cognitive processes with the goal of helping individuals reduce self-defeating behaviors (such as problematic substance use or negative thinking patterns) and increase and maintain health behaviors. Examples include managing negative thinking, identifying and altering cognitive distortions, communication skills, decision-making skills, stress management, and time management. CRA is an extension of CBT, designed to help individuals establish and maintain new healthy patterns of behavior and leverage social, recreational, family and vocational reinforcers to help them in making positive behavior change.

4. Offer support (or "reinforcement") of successes in behavior change from an online support network of the user's choosing (e.g., friends, family) (another key component of **CRA**).[42, 43]

Based on these scientific approaches, Laddr initially is structured as a "**process loop"** that includes a **"discovery"** process to help end users identify values/goals and motivate progress toward goals, such as diet, activity level, smoking and/or recreational goals (BA), an **"action"** process to track (in real time) progress toward goals, functioning, chains of health behavior/medical regimen adherence (or lapses in health behavior), a **"remediation"** process to access any of over 70 "guides" (delivering interactive CBT/CRA) based on end user needs/preferences, and **"reinforcement"** functionality to reinforce progress toward goals and health behavior.[44, 45]

Evidence-Base. The efficacy of this approach to treat depression has been supported in numerous randomized controlled trials, including studies conducted in primary care and medically ill populations. Meta-analyses have shown consistently strong effect sizes of this approach in increasing depression-free days by as high as 50%. This approach also markedly reduces depression symptoms and improves functioning. This work has also demonstrated that this approach to depression care creates a level of therapeutic affiliation (an essential component of psychotherapy) equivalent to live therapy. This approach also has been shown to be cost-effective by decreasing medical care expenditures and increasing work productivity.[37, 46, 47]

The functionality of Laddr has been shown to be *as effective as* science-based, behavioral therapy delivered by highly trained therapists in promoting objectively measured abstinence from substances of abuse.[48] It has also been shown to *double abstinence rates* compared to standard substance abuse treatment delivered in the U.S. (which may not always be science-based).[49, 50] This program has been shown to be more effective than traditional treatment models for even the most challenging of cases– including persons who have a history of chronic relapse to substance use, persons with high

ambivalence about changing their problematic substance use, and persons with high anxiety.[51, 52] The effectiveness of this system has been shown with a wide array of persons with problematic substance use, including use of alcohol, opioids, cocaine/other stimulants, marijuana, and poly-substance use.[50]

Note that the applicant team is in the process of creating a version of Laddr in Spanish to function as described above for Latin American communities. Although we will conduct pilot testing with a wide array of stakeholders in the proposed project (described below) in which we will evaluate and refine this system before and after it is deployed, we did not seek funds in the budget of this project – which is focused on implementation science and capacity building-- to complete our Latin American version of this mobile ecosystem.

(2) Workforce Training in new Service Delivery Models. Primary care is the main source of healthcare for most persons in Colombia and elsewhere in Latin America, including for the poorest citizens. Turnover rates of primary care physicians is high, with many physicians remaining in their position at a given program for less than 2 years. However, nurses and social workers tend to remain in their positions much longer. Although mental health care may be available via specialty referral, wait lists for mental health specialty programs often exceed 2 months.[53]

Our team (under the leadership of Multiple PI Gómez and Consultant Uribe) has extensive experience conducting mental health training among healthcare providers in Latin America.[54-57] Our workforce training plan will be based on these prior successes as well as similar models that have been shown to be successful in training the primary care workforce in Latin America.[53, 58, 59]

Specifically, the training will be available to all levels of providers in our partnering primary care sites, including one training for nurses, nurse assistants, social workers and health promoters and a second training for general physicians and chief nurses. Trainings for the first group will entail a 16 hour, in-person mental health training, followed by access to virtual training support. Trainings for the second group of physicians and chief nurses will be shorter, given their time constraints and given the plan for the first group of healthcare workers (who remain in their roles in primary care longer) to largely assume responsibility for screening/embedding depression care into primary care. The training will focus on mental health disorders in primary care and screening strategies for detecting mental health problems – with a primary focus on integrating depression screening and care into primary care. A secondary focus will be on alcohol and substance use and its relation to depression. This work will be based on clinical practice guidelines developed by Dr. Gómez and Dr. Uribe and their team at the Pontificia Universidad Javeriana and refined in collaboration with the present applicant team as part of the formative work the team has conducted over the past several years. Typical clinical case histories will be used as examples for training and learning evaluation. Consistent with models Dr. Gómez and his team have previously used, the virtual training component will consist of a set of computerized education modules with built-in quizzes to assess learning (offered on a platform at Pontificia Universidad Javeriana). Dr. Gómez will take the lead on creating the content for these online educational modules, along with his course development team at Pontificia Universidad Javeriana, as he has done in the many prior courses created by his group.

Trainings for the first group include 7 main modules on topics of: (1) Introduction and conceptual bases to mental health; (2) How mental health care works within primary care and within the broader healthcare system; (3) Community processes in primary care; (4) Network identification and characterization for community action; (5) Support tools and methods for screening and defining care

pathways; (6) Support interventions -- Emotional "first aid" including brief and group interventions; and (7) Community based mental health rehabilitation. The abbreviated training for the second group includes 5 main modules on topics of: (1) Introduction and conceptual bases to mental health; (2) Community Processes in Primary Care; (3) Interviewing patients with mental health problems; (4) Conducting a clinical history for mental health; and (5) Early detection, diagnosis and management of mental health disorders.

Note that we will also train this clinical workforce at each partnering primary care site on the Laddr mobile platform. While Laddr has been developed to be intuitive and self-driven, we will ensure that at least one person at each site can provide first-line technical assistance as needed (also with the help of the technical assistance staff person at Pontificia Universidad Javeriana who will provide support to all partnering primary care sites and serve as a valuable resource for consultation (e.g., if challenges with Internet connectivity arise).

Trainings will be conducted prior to implementation of the mental health service delivery model at each of our partnering primary care sites (see chart of Timeline/Milestones below). We anticipate training approximately 5-25 nurses, nurse assistants, social workers and health promoters at each site and training about 3-10 general physicians and chief nurses at each site. [Note the wide range in the number of trainees per site reflects the varying sizes of study sites across urban and rural settings]. Dr. Gómez (an expert in depression care) and a psychiatrist on this project at Pontificia Universidad Javeriana will lead the trainings. Each individual who completes the training will receive a certificate (diploma) for this course from Pontificia Universidad Javeriana. Dr. Gómez has similarly issued certificates for many prior workforce training programs he has led.

(3) Integrated Data Management System. We will create an integrated data management system for this project for systematic data tracking and outcomes assessment. Participants' completion of study assessments will be completed via an encrypted Internet connection via 128-bit Secure Sockets Layer (SLL) - the standard technology for securing eCommerce and eBanking transactions on the Internet. We plan for all these project data to be coordinated through REDCap (Research Electronic Data Capture),[60] which we intend to set-up at our partnering university in Colombia, Pontificia Universidad Javeriana. The REDCap Consortium is composed of 1,520 active institutional partners in 92 countries who utilize and support REDCap in various ways. Both Dartmouth and Javeriana will have access to REDCap and the data collected in this project (via web-based access). We will set-up data monitoring/sharing access privilege to ensure the integrity of data collection/management (under the leadership of Senior Data Manager Mary Ann Greene at Dartmouth).

We will seek Institutional Review Board (IRB) approval at Dartmouth as well as from Pontificia Universidad Javeriana and any partnering health care systems, as required. Any reportable events will be reported to both Dartmouth's and Javeriana's IRBs. Our data management expert at Dartmouth (Mary Ann Greene) will serve as an expert advisor on data management systems broadly and REDCap specifically.

(4) Learning Collaborative. As primary care programs join the implementation project and launch the proposed novel mental health service delivery model as part of their model of care, they will be able to join a learning collaborative of all sites implementing this model. This learning community will meet quarterly by webinar and share lessons learned – including successes and challenges in implementation. These meetings will be in addition to the once per year in-person meeting in which these individuals

will participate. Data collected at each site will be aggregated by site (by the Dartmouth team) for review and discussion at this quarterly meeting. Quarterly meetings of this learning community will be co-led by Multiple PI Gómez and Consultant Uribe. Learning collaboratives have been shown to be highly effective in promoting shared learning among a broad community.[61]

9.0 STUDY POPULATION FOR IMPLEMENTATION STUDY

9.1 Provider and administrative staff Inclusion Criteria:

- Aged > 18 years
- Have worked for the study site for at least 3 months.

9.2 Participant Inclusion Criteria:

- Aged ≥ 18 years
- Patients at one of our collaborating primary care sites
- Screen positive for minor (score of 5-9), moderate (score of 10-14), moderately severe (score of 15-19) or severe (score of 20-27) depression on Patient Health Questionnaire (PHQ-9)[62] **and/or** screen positive for problematic alcohol use on Alcohol Use Disorder Identification Test (AUDIT) developed by the World Health Organization (a score of 8 or more on 10-item AUDIT)[63] **and** have a confirmed diagnosis of depression and/or alcohol use disorder based on clinical consultation at the primary care site
- Willing to provide informed consent to use mobile intervention and complete study assessments

9.3 Participant Exclusion Criteria

- Diagnosis with co-occurring severe mental illness (e.g., schizophrenia, bipolar disorder, depression with psychotic features)
- Alcohol withdrawal symptoms that require higher level of care (e.g., emergency medical or inpatient treatment)
- Express suicidal intention. This assessment will be based on a combination of a patient's response on the PHQ-9 assessment followed by further assessment by a primary care clinician. The PHQ-9 measure will not be used solely to determine eligibility on this criterion. Persons who express suicidal intention will immediately be provided immediate crisis management in accordance with the crisis management protocol at the collaborating primary care site.
- Intoxicated or otherwise impaired at the time of assessment (rendering them incapable of informed consent)

No Sex/Gender or Racial/Ethnic groups will be excluded. Based on patient data at our partner sites, we expect that approximately 65% of the participants will be women. And, we expect that approximately 60% will be white, 10% will be black, and 30% will be a mixture of other racial groups.

Note that individuals will not be excluded if they do not have access to smartphones. Although the mobile therapeutic tool that will be offered to participants as part of this project is not accessible on feature phones (non-smartphones), it is web-based and can be accessed on tablets or other types of computers. Although patients are likely to most benefit from mobile access to the intervention (for

anytime/anywhere access), each collaborating study site will set-up computers at their site to allow patients to access the mobile intervention onsite if they so choose.

9.4 Participant Recruitment, Screening and Informed Consent

Administrative staff at the partnering primary care site who "check-in" patients upon arrival will ask each adult to complete the screeners (for depression and problematic alcohol use) at the time of check-in. Screening for depression and problematic alcohol use will become standard practice at all collaborating sites. So, all patients at the site will be screened regardless of their participation in the study. Screeners will be administered via paper or tablet (according to patient preference and site capability) in the waiting room. Note that patients who are already actively participating in the study will not be asked to complete this screener at check-in.

The screener for depression will start with the two questions on the Whooley assessment [64]: (1) "During the last 30 days, have you been bothered by feeling down, depressed or hopeless (YES/NO)?"; (2) "During the last 30 days, have you been bothered by little interest or pleasure in doing things (YES/NO)?" A positive response on either or both questions will then lead to a Patient Health Questionnaire (PHQ-9)[62] screener for depression.

The brief screener for alcohol, the Alcohol Use Disorder Identification Test Alcohol Consumption Questions (AUDIT-C)[65], consists of 3 questions: (1) "How often do you have a drink containing alcohol?" (Never; Monthly or less; 2-4 times a month; 2-3 times a week; 4 or more times a week); (2) "How many standard drinks containing alcohol do you have on a typical day?" (1 or 2; 3 or 4; 5 or 6; 7 to 9; 10 or more); and (3) "How often do you have six or more drinks on one occasion?" (Never; Less than monthly; Monthly; Weekly; Daily or almost daily). The AUDIT-C is scored on a scale of 0-12. In men, a score of 4 or more is considered positive, and in women a score of 3 or more is considered positive, which can assist with identifying problematic alcohol use. Persons who answer positively to the AUDIT-C questionnaire will then be asked to complete the full Alcohol Use Disorder Identification Test (AUDIT)[63] to screen for alcohol use problems.

Screening results will be provided to the primary care clinician (by the administrative staff or clinical intake worker) either prior to, or at the time when, the patient enters an exam room to see the primary care clinician. Given the state of the electronic health records at participating sites (e.g., some do not have them), we do not envision that tablet results will be directly entered into the electronic health record (although this may evolve over the life of the project). The administrative staff worker or clinical intake worker will score the results on each screener before the patient sees the primary care clinician (unless scoring is automatically done on a computerized screener). Both the responses to individual screener questions as well as the scored results will be provided to the clinician (including designations of mild, moderate, moderately severe and severe). A suicide risk assessment will be conducted by the clinical staff if item 9 of the PHQ-9 is positively answered or if deemed otherwise clinically important by the clinician during examination. Each site has an internal protocol for evaluating and managing suicide risk as identified on the PHQ-9 or in discussions between a patient and clinician. Specifically, in this process, each site follows Colombian guidelines in which a clinician asks the following questions about suicidal ideation, plans, gestures, and attempts, or behaviors of self-harm (to identify any patient needing immediate psychiatric or emergency referral):

1. Do you feel worth living?
2. Do you want to be dead?
3. Have you ever thought about ending your life?

4. If so, have you thought about how you would do it? What method would you use?
5. Do you have access to a way to carry out your plan?*
6. What prevents you from getting hurt? Do you feel worth living?

In the event of a positive screen for depression and/or alcohol use problems, the clinician at the primary care site will complete a more in-depth diagnostic interview to better understand the data provided by patients on the screeners. Participants who screen positively for depression (score of ≥ 5) and/or alcohol use problems (score of ≥ 8) and meet all other inclusionary criteria will be informed about the treatment options available to them under this project in which the site is participating. As part of this process, the primary care clinician (or his/her designee at the primary care site) will inform patients about the goals of the project, the types of services they would be offered as part of the project and what patients would be asked to do if they elect to participate (e.g., use digital therapeutic tool for supporting mental health; complete period assessments over time). A research staff member or a clinician at the study site will provide participants with an informed consent form to participate in the study. We intend to ask participants to complete consent forms electronically within REDCap. Participants will also receive a blank paper copy of the consent form for their reference (and for research contact information on the form). This process is consistent with requirements of Dartmouth's IRB. Patients who provide informed consent will then be asked to complete baseline participant assessments (described in section 12.0 of this protocol). Details of the Informed Consent process are included in Section 15.4. The research team will only track outcomes from patients who provide a signed study consent form.

Note that patients who elect to join the study will be advised in the consent form that the research team would like to be able to access their screening data collected in their medical record before study consent (for depression and problematic alcohol use) for inclusion in the research data. We will also obtain data on patients' attendance records at the primary care study site.

All patients who join the study will be assigned a unique study identification number (which will be linked to all patient data collected from a given participant). The percent of patients who are eligible to participate but who decline participation will be tracked, along with patients' reported reasons for non-participation. These data will be collected at each collaborating primary care site but will be tracked centrally across all sites. These data will help the project team better understand the acceptability of the model of care being offered in this project and help the team consider modifications to the implementation model to improve the model of care, as needed.

At the end of their study period, participants will be given in person (or emailed if the participant has already completed their follow-up visit and we are unable to give them their letter in person) a close-out letter that thanks them for their participation in the study, encourages them to continue seeking treatment for their medical condition, and provides them with a link to the DIADA project where they eventually will be able to view aggregate study results. These letters will be stored on a password-protected study computer and in the study's regulatory binder, which is stored in a locked filing cabinet.

To mitigate any potential increased risk of loss of confidentiality, we will 1) only email letters if we are unable to give participants their letter in person 2) email instead of mail these letters to reduce the risk that anyone other than the participant sees the letter 3) ensure that the email address to which we send these letters is personal to the participant, rather than a shared email.

Patients who decline to participate but who may have severe depression or suicide risk will be treated in accordance with each clinical site's suicide risk management policies. The patient's primary care physician will be informed about the results of the screening and the patient will be managed according to the primary care site's usual protocols and guidelines.

Consistent with the goal of this project, patients will be offered a multi-component model of science-based mental health care. All participants who consent to participate will be given access to the mobile therapeutic tool. A trained staff member at the primary care site will show them how to use the tool. As noted above, participants will be offered the option to access the tool on their smartphones. Additionally, or as an alternative to smartphone access, patients will be offered the opportunity to access this web-based resource at one of several computers that will be set-up at the primary care site (likely 2-4 computers per site). Note we have included WiFi/hotspot/router set-up costs in the study budget for select sites (e.g., rural), as needed.

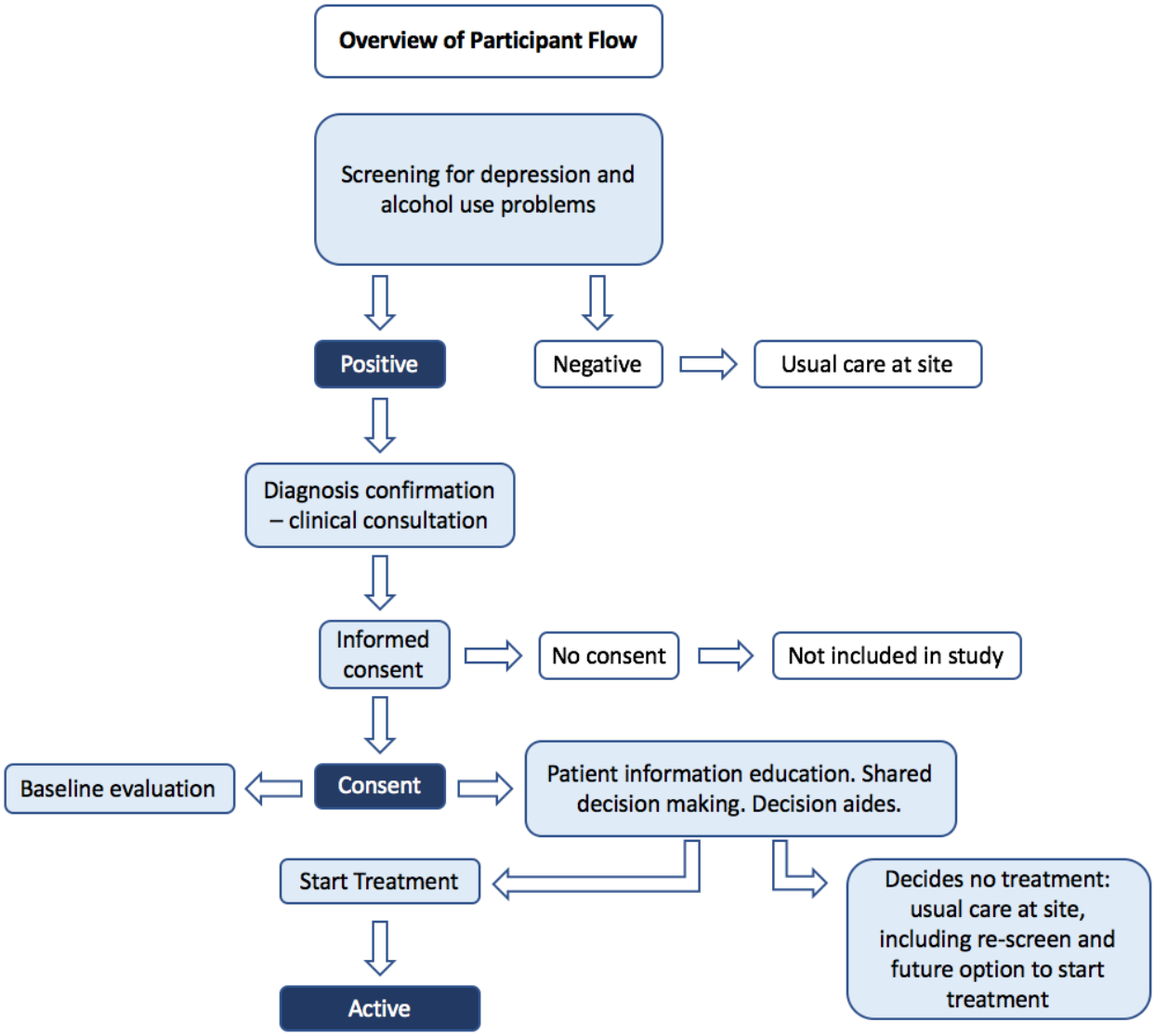
All participants will be encouraged to access community-based resources for depression and/or problematic alcohol use, when available. For example, participants may be informed of local Alcoholics Anonymous meetings or other substance use/mental health support groups available in their communities. Participants may also be referred to speciality mental health care (e.g., psychologist or other mental health worker); however, we expect few participants will engage in such care due to its very limited availability in most settings in Colombia.

Participants diagnosed with depression (particularly moderate to severe depression) may also be offered access to anti-depressant medications, as determined in consultation with the primary care physician. Medication prescribing for depression will be conducted in accordance with the Colombian clinical guidelines of best practices. Medications for treatment of alcohol use disorders are not currently available in Colombia. If they become available during the course of this project, we will modify the protocol, as appropriate, to embrace evidence-based medications for the treatment of alcohol use disorders.

If a patient meets criteria for severe depression, or has significant suicide risk, treatment may be either done by, or coordinated with, a psychiatrist (in accordance with the Colombian clinical guidelines of best practices).

We plan to develop a printout of a decision aid tool for clinicians to use, designed as a matrix to help patients understand the various options available to them as part of their care (including the advantages and disadvantage of the various options). We may also develop a video or other educational resources to help patients understand how the various care options available to them work to support a process of shared decision-making.

The flow of participant activity is summarized in the accompanying figure.

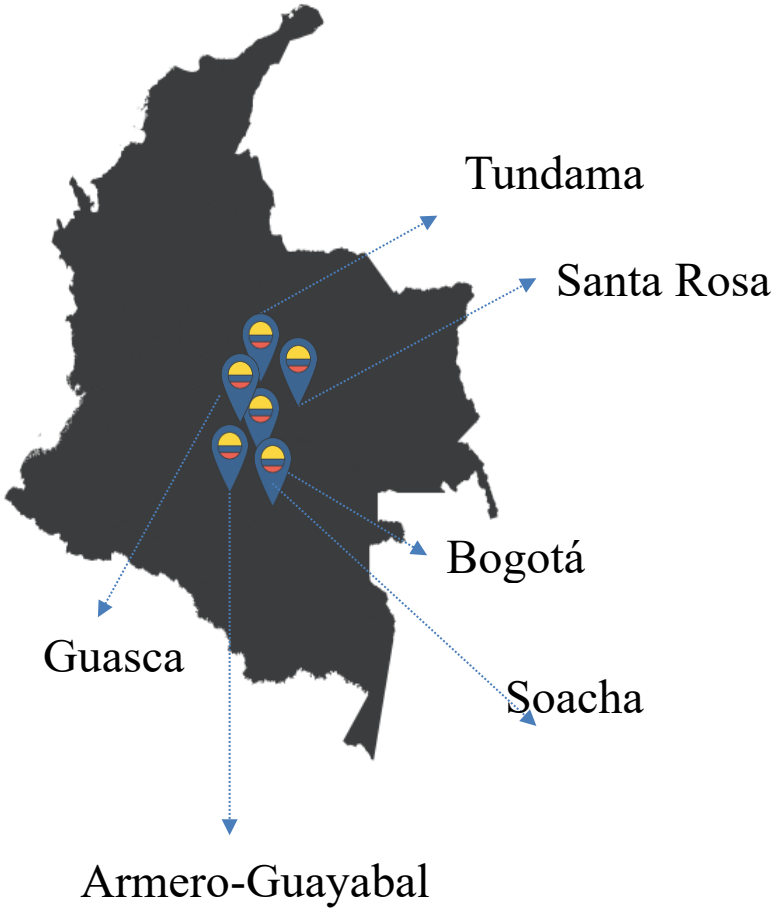


Note that as detailed in the section 15.4 on Informed Consent, both provider and administrative staff at partnering primary care sites will all be offered the opportunity to complete the implementation context and outcome measure in this research project (including nurses, nursing assistants, social workers, health promoters, physicians and charge nurses, program administrators). All participating staff will also be asked to provide consent to participate. Provider and administrative staff all need to be aged ≥ 18 years and have worked for the study site for at least 9 months. Research staff will provide informed consent to each staff member. We expect approximately 4-8 provider staff per site will complete the provider measure of implementation context and outcomes and about 2-5 administrator staff per site will complete the organizational level measure of implementation context and outcomes at each timepoint.

10.0 SITE SELECTION

10.1 Number of Sites

We will collaborate with 6 primary care networks spanning diverse rural and urban locations across three states in Colombia: (3) Cundinamarca (Javesalud, Soacha, Guasca), (2) Boyacá (Santa Rosa, Tundama) and (1) Tolima (Armero-Guayabal). [See Colombia map below]. None of these primary care systems routinely screen for/treat depression or alcohol use disorders within their primary care programs. The Bogotá site (Javesalud) will serve as the pilot study site and will remain a study site thereafter.



10.2 Site Characteristics

Fundación Javeriana de Servicios Médicos ondontológicos inter-universitarios (The Javeriana Foundation of Inter-University Odontologic Medical Services) "Carlos Marquez Villegas" Javesalud
Javesalud is a Colombian ambulatory health center that focuses on patient-centered primary care within a family medicine framework (working with children, adolescents, adults and pregnant women). Javesalud has 7 outpatient primary care program servicing over 95,000 individuals in Bogotá, Colombia.

Empresa Social del Estado Hospital Regional de Duitama - Santa Rosa de Viterbo Branch
Santa Rosa de Viterbo Regional Branch offers primary care ambulatory services (outpatient, emergency care, ambulance transportation) covering a population of 14,000 persons, 47% of whom live in rural areas. It also provides general medical and psychological services.

Salud de Tundama

Salud de Tundama is a health organization that offers primary care outpatient services, self-care promotion and risk management for adult and child populations in Duitama and in the surrounding area. It provides low complexity general medical services such as pre-conception education, promotion and prevention programs, basic laboratory tests, and vaccinations.

Empresa Social del Estado San Antonio Guativa
The Guasca hospital is a public healthcare center that is affiliated with Hospital San Antonio in Guatavita. The hospital has about 4 general practitioners and serves around 110 patients daily. Guasca is a town located in Cundinamarca, about 2 hours from Bogotá DC, with about 15,000 inhabitants; 60% of them live in semi-urban areas.

Hospital Armero-Guayabal (Empresa Social del Estado Hospital Nelson Restrepo Martinez)
Armero-Guayabal Hospital provides primary care and ambulatory, emergency and short stay hospitalization services covering the population for the municipality of Armero-Guayabal and its rural counties.

Empresa Social del Estado Hospital San Juan Bautista
The Soacha hospital (the Hospital Mario Gaitán Yanguas) is a public healthcare center that is affiliated with the Health Secretary from the Department of Bogotá. The Soacha hospital has 10 general practitioners and serves about 300 patients daily. Soacha is a town located in Cundinamarca, about one hour from Bogotá DC. Soacha is part of the metropolitan area of Bogotá DC, with about 556,268 inhabitants. 99% of the population lives in urban areas.

10.3 Rationale for Site Selection

These sites were selected to add diversity of primary care sites and participants across multiple states and regions of Colombia. These sites span urban and rural contexts (including farming communities). They also provide diversity in access to/usage of mobile technology. All of these parts of Colombia are burdened by limited access to mental health screening and resource delivery and thus all of these communities may benefit from the project. Including these diverse sites enhances the generalizability of study findings.

Additionally, as noted above, Javeriana has an academic partnership with Javesalud (which is only about 30 minutes from Javeriana). Javeriana also has an academic partnership with Empresa Social del Estado Hospital Regional de Duitama - Santa Rosa de Viterbo Branch. Javeriana does not have pre-existing academic partnerships with the other sites but has already established relationships and confirmed commitments of collaboration from the leadership of those sites. Javeriana also has multiple interns that complete some of their training at these sites.

10.4 Wi-Fi Expansion to Rural Sites

The government of Colombia has recently launched a plan to increase the availability and use of information technologies across the country in a plan called "Vive Digital 2014-2018."[66] In this plan, Colombia aspires to become a leader in the use of social apps for the poorest, and its goal is to become the first country in Latin America with wide-reaching high speed Internet. In 2014, 1,078 municipalities in the country were connected through the high speed fiber optic Internet. The plan also has a goal of achieving 4G WiFi in 1000 zones across the country and increasing by 4-fold the number of persons with

mobile Internet by 2018. Relatedly, in the health sector, the implementation of a unified unique electronic health record is also a national priority. However, we will help enable Internet connectivity at partner sites as needed (e.g., rural locations) and have budgeted resources in our NIMH study to support this.

11.0 STUDY PROCEDURES

11.1 Pilot Implementation Study

We will launch a pilot implementation project at a single site (Javesalud primary care site). We aim to launch this pilot project in the summer of 2017.

In this process, we will train staff at the site in accordance with the workforce training plan described above, set-up the data management system described above, and include up to 50 patients at the site who meet diagnostic criteria for depression who have access to this new mental health service delivery model (including Laddr access).

As part of the workforce training (described above), clinicians will be trained on the standardized screeners of depression and alcohol use. As reviewed above, study participants who are identified as meeting criteria for depression and/or problematic alcohol use will meet with a mental health-trained clinician at the primary care site and offered access to the mental health resources described above.

The outcomes to be measured in this pilot include the original measures and assessment timepoints detailed in version 8.0 of the protocol (e.g. they include the Alcohol TLFB instead of the QDS and include the ED-5D). As the central focus of this pilot is to identify any challenges in implementation, we will use information that we learn from the pilot to modify our assessments and assessment timeline for the full implementation trial. This pilot project will allow us to refine the mental health service delivery model as well as the content of the Laddr platform as needed before expanding implementation within Javesalud as well as at other sites. However, in order to maintain continuity of data within the pilot, we will contain to measure follow-up assessments for the pilot using the measurements and assessment timeline detailed in version 8.0 of the protocol. This will allow us to compare data collected from participants in the pilot study across multiple timepoints.

11.2 Implementation Research

At the completion of the pilot phase, we will expand our implementation across multiple Colombia-based primary care sites in urban and rural communities (using the same procedures described for the pilot above).

Consistent with a modified stepped wedge design (multiple baseline design),[18, 19] we will implement across sites on a staggered basis and expand the number of sites in which we implement over time. Specifically, all sites will complete core organizational measures (described below) every 6 months to a year depending on the measure. And then we will launch at our second primary care site in the fall of 2018; Site 3 will launch in the spring of 2019; Site 4 will launch in the fall of 2019 and the final 2 sites will launch in the spring of 2020. We plan for about a six month time window between the launch of implementation activities across sites.

We have engaged key leadership at all participating sites from the initial project kick-off meeting we held in Bogotá, Colombia in September 2016. And, we continue to engage with them regularly as part

of our formative research activities. This ongoing dialogue about project activities will help expedite the launch of implementation research at each of our collaborating sites.

Using the primary care site as the unit of analysis,[67] the single-subject approach offered via the stepped-wedge design will enable the repeated measurement of outcomes at the organizational level, including aggregated effects on clinicians, patients, and practices. In this single-subject, stepped-wedge design, each site acts as its own pretest control (from baseline data collection). During the data collection period, core organizational indicators (as described in Section 12.0) will be assessed every 6 months.

Note that we considered conducting an experimental randomized controlled trial, but based on the goals of this implementation science and capacity building research project, we elected to use this design to balance rigor in the design with creating real-world sustainable models to scale-up mental health service delivery in Latin America.

This stepped-wedge design offers advantages compared to randomized controlled trials.[68] This design costs less than randomizing a large sample of organizations required to run the inferential statistics associated with randomized controlled trials (or cluster randomized trials). It makes it easier to understand the dynamics of change processes (such as implementation) than randomized, controlled trials do. It avoids the ethical problem in randomized, controlled trials of withholding interventions from a proportion of participants who might benefit. Further, given the project's goal of scaling-up and sustaining evidence-based mental health care in Latin America, providing the novel intervention to as many sites as possible is ideal (which would not have been possible in a randomized, controlled trial). Additionally, a stepped wedge design allows us to train study site staff in mental health screening and care delivery, which enhances the potential for sustainability of this care model.

The single-subject approach emphasizes recurrently tracking behaviors and practices in a "repeated time series"[69, 70] that permits the study of change patterns. The stepped-wedge designs that often accompany single-subject studies provide the intervention to all participants, but isolate the independent variable by introducing the intervention at specified points.[71]

As described in the Capacity Building core of this application, in Year 5, we will conduct trainings to launch implementation efforts in the countries of Chile and Peru (at least 2 sites per country). These additional countries will have participated in the learning collaborative from years 1-5. We will additionally evaluate the ongoing sustainability and/or expansion of the novel service delivery model both within Colombia and elsewhere in Latin America. Given that numerous stakeholders in the region will be participating in the evolution of this work from its inception and throughout the entire process (including payers who may embrace this approach within their business model), and given how this work may allow Latin America to help realize their goals and stated policies on scaling up mental health care within primary care sites, we may observe growth of this model over time beyond what is explicitly planned in this project.

The **timeline** below shows the planned staggered implementation across collaborating primary care sites.

	Javesalud	Santa Rosa de Viterbo	Salud de Tundama	Guasca	Armero-Guayabal	Soacha	MONTH
Year 2							
Aug-17	BHIMC	BHIMC			BHIMC		**0**
Nov-17	IMICO, PSAT, TDABC						3
Feb-18	Site Launch						**6**
Mar-18		TDABC			TDABC		7
May-18		Provider training, IMICO, PSAT					9
Year 3							
Jul-18	Qualitative Interviews						11
Aug-18		Site Launch, BHIMC					**12**
Sep-18							13
Nov-18	IMICO, PSAT	Qualitative Interviews					15
Jan-19			Provider training				17
Feb-19	Qualitative Interviews BHIM	Qualitative Interviews, IMICO PSAT	Site Launch, BHIMC, TDABC, IMICO, PSAT	BHIMC, TDABC	TDABC, BHIMC	TDABC, BHIMC	**18**
May-19			Qualitative Interviews	Provider training, IMICO, PSAT			21
Year 4							
Aug-19	IMICO, PSAT	IMICO, PSAT, BHIMC, TDABC	Qualitative Interviews, IMICO, PSAT	Site Launch, BHIMC, TDABC			**24**
Nov-19				Qualitative Interviews	Provider training, IMICO, PSAT	Provider training, IMICO, PSAT	27
Feb-20	IMICO, PSAT, BHIMC, TDABC	IMICO, PSAT	IMICO, PSAT, BHIMC, TDABC	Qualitative Interviews, IMICO, PSAT	Site Launch, BHIMC, TDABC	Site Launch, BHIMC, TDABC	**30**
May-20					Qualitative Interviews	Qualitative Interviews	33
Year 5							
Aug-20	IMICO, PSAT	IMICO, PSAT, BHIMC, TDABC	IMICO, PSAT	IMICO, PSAT, BHIMC, TDABC	Qualitative Interviews, IMICO, PSAT, BHIMC, TDABC	Qualitative Interviews, IMICO, PSAT, BHIMC, TDABC	**36**
	*Patient measures for the full implementation study are collected at baseline and every three months thereafter for a period of 12 months (5 time points). Measures include: PHQ-8, QDS, WHODAS, GAD-7, NSMOS/NMED. The HPQ is administered every 6 months. The ED-5D and TLFB are only collected for pilot participants	**Qualitative Interviews include: Administrative interviews, provider interviews, and patient interviews					

11.3 Participant Reimbursement

Participants in the implementation trial will not be compensated for their participation with the exception of the small group of participants who agree to participate in qualitative interview data collection (who will receive a gift card equivalent to $10 USD after each interview).

12.0 STUDY ASSESSMENTS

In accordance with our planned stepped-wedge (multiple baseline) design, we expect to complete the implementation measures of the Behavioral Health Integration in Medical Care Index (BHIMC) measure and the Time-driven activity-based Costing Approach measure (TDABC) approximately every year prior to the time of implementation launch at a given site (starting with baseline in the spring of 2017); at the time of implementation launch; and approximately every year thereafter at each site. We plan to administer the implementation context and outcomes measure (with providers and organizations) shortly after they have been trained in the model of care (approximately 3 months before site launch at a given site) and approximately every 6 months thereafter at each site from the start of the site's launch

Most participant-level assessments will be completed at the time a patient joins the study and every 3 months thereafter. The Integrated Measure of Implementation Context and Outcomes in Low and Middle Income Countries will not be administered to patients at baseline and will be administered at six

month intervals instead of three month intervals, given the lack of sensitivity of the measure to change over short periods of time. The Health and Performance Questionnaire (HPQ) will be also be administered at 6 month instead of three month timepoints, given the length and patient burden of the measure.

12.1 Quantitative Outcome Measures

12.1.1 Summary of Quantitative Outcome Measures

We will measure the ability of our proposed approach to accelerate the translation of evidence-based mental health services into practice and expand research capacity at multiple levels, including the following **implementation outcomes:**

(1) Ability to accelerate the adoption of science-based mental health service delivery (including its ability to increase provision of evidence-based mental health resources to more individuals)

(2) Acceptability as a model of healthcare service delivery (the ability of the technology-based service-delivery model to increase patient activation and engagement in their own self-management)

(3) Cost-evaluation of services in the model

We will also collect **patient level data outcomes** to assess:

(4) Impact on public/population health (including its effects on accelerating improved behavioral health and health outcomes, and improving patient quality of life and functioning).

Implementation and Patient level outcomes are detailed below.

To promote an understanding of contextual facilitators and barriers to successful implementation of technology-based treatments, a common framework for measurement of implementation factors and implementation outcomes is needed so data can be meaningfully synthesized and interpreted across studies. Such harmonization of measurement has been strongly heralded by behavioral treatment development and implementation science researchers as critical to moving the fields forward.[72-75]

Overall Framework for selection of implementation measures. We will use the Consolidated Framework for Implementation Research (CFIR;[76] Damschroder et al., 2009) as an organizing framework to guide compilation of measures to evaluate barriers and facilitators to implementation in each of the following domains: intervention characteristics, organization characteristics (e.g., climate, readiness), individual characteristics (i.e., provider/staff attitudes, experiences; patient attitudes and experiences), and external influences (e.g., socio-political characteristics, local technology infrastructure i.e., wireless in the community, state policy/regulations, and reimbursement models). Strategies related to planning, facilitating provider and patient engagement in use of the novel mental health service delivery model, and potential sustainability issues will also be explored.

We will focus generally on three categories of implementation outcomes for inclusion in the assessment battery: penetration (i.e., the extent of integration of the innovation within a service setting and its subsystems), acceptability (i.e., perception among stakeholders that intervention is acceptable) and costs (i.e., resources and unit costs).

12.1.2 Quantitative Implementation Measures

Integrated Measure of Implementation Context and Outcomes in Low and Middle Income Countries. We have worked with our diverse group of stakeholders to review existing measures for the implementation context and outcome constructs. We have compiled existing measures based on available meta-analyses and systematic reviews of the literature,[77] as well as existing, and growing, repositories of measures related to health services implementation science.[78, 79] We have reviewed potential measures based on psychometric properties, use across diverse populations, predictive validity for implementation outcomes, and extent to which they are practical and easy to use within diverse settings.[80]

During the course of this process, we identified a measure that captures our broad array of planned implementation metrics which has been used extensively in multiple low and middle income countries. This metric was developed by the lead investigators of the NIMH-funded hub working in Myanmar (led by Drs. Murray and Bass at Johns Hopkins University, with whom we have consulted extensively on the use of this metric in our project in Latin America). This measure was specifically designed to measure implementation factors of relevance in low and middle income countries which are not reflected in U.S.-based implementation metrics.[81] **This measure, composed of a Consumer (patient) instrument, a Provider level instrument, an Organizational Staff level instrument and a Sustainability instrument will be our primary quantitative assessment tool in this project.**

The **Consumer** (patient) instrument consists of scales to measure Acceptability (17 items), Adoption (12 items), Appropriateness (13 items), Feasibility (14 items), and Penetration (8 items). The **Provider** level instrument contains 16 items to measure Acceptability, 9 items for Adoption, 16 items for Appropriateness, 20 items for Feasibility, 8 items for Penetration and additional scales to measure Organizational Climate (13 items), and Organizational Leadership (10 items). At the **Organizational Staff** level there are 10 Acceptability items, 13 Adoption items, 12 Appropriateness items, 14 Feasibility items, 8 Penetration items, 15 Organizational Climate items and 10 Organizational Leadership items. Each scale is scored on a 4-point ordinal scale ranging from *0* "not at all" to *3* "a lot," with an additional category for "don't know/not applicable."

In addition, the **Sustainability instrument** was adapted from the Program Sustainability Assessment Tool (PSAT). The original PSAT is a 40-item instrument used to assess a program's current capacity for sustainability across a range of organizational and contextual factors.[82] The goal of the PSAT is to identify barriers and facilitators to program sustainability, which can be used to guide development of a sustainability action plan.[83] The PSAT was developed based on a literature review of 85 studies focused on sustainability of public health programs. Data from these studies identified eight core domains that affect a program's capacity for sustainability. These domains include: environmental support, funding stability, partnerships, organizational capacity, program evaluation, program adaptation, communications, and strategic planning.[84] It has demonstrated internal consistency reliability, structural validity and usability.[82, 85]

Background to Development of Consumer, Provider, Organizational Staff Level and Sustainability Level Implementation Measure for Low and Middle Income Countries (LMICs). Colleagues leading an NIMH research hub in Myanmar extended their long-standing work in adapting and testing mental health measures across cultures and contexts[86-88] to adapt and develop measurement instruments to study implementation of mental health programs in low and middle income countries.

Based on results from an initial study using implementation measures developed in the US to study the implementation of evidenced-based mental health programs in Zambia, Iraq and Thailand, they determined that there was a need for new implementation science tools. The implementation measures developed in the US, even though adapted, showed inadequate psychometric properties, were reported to be impractical for regular use, had multiple items that did not work well in the study contexts (e.g. questions about insurance reimbursements, automated billing, etc.), made assumptions about underlying health care systems (access to regular training and educational material, accreditation agencies, etc.), did not tap into relevant implementation outcomes (i.e. Proctor et al. 2011),[73] and were not applicable across multiple stakeholder levels.

In response, the team developed a measure (The Integrated Measure of Implementation Context and Outcomes in LMICs) based on the implementation science outcomes of Acceptability, Adoption, Appropriateness, Feasibility, Sustainability and Penetration.[73] Instruments were populated through several steps: 1) careful delineation and operationalization of outcomes in the context of low and middle income countries; 2) review of three leading implementation science frameworks: Consolidated Framework for Implementation Research (CFIR)[76]; the Reach, Effectiveness, Adoption, Implementation, and Maintenance framework (RE-AIM)[89]; and the Exploration, Preparation, Implementation and Sustainment (EPIS) framework[90]; 3) consultation with experts in the field of international health, health systems, global mental health, and implementation science; and 4) use of logistical frameworks to draft each instrument and link them to overall program goals.

Their new instruments were tested using mixed methods as part of a project focused on scale-up of evidence-based mental health programs in Iraqi, Kurdistan and Myanmar. Questions related to adoption and sustainability were explored qualitatively only. The reliability and construct validity of the instruments were tested among consumers (N=155 in Kurdistan; N=157 in Myanmar), mental health providers (N=26 in Kurdistan and Myanmar), organizational level staff (N=52 in Kurdistan; N=4 in Myanmar), and policy level personnel (N=12 in Kurdistan; N=4 in Myanmar). Results indicated that questions were easily translated and understood. Reliability results showed adequate internal consistency reliabilities for all provider level scales across settings (Chronbach's Alphas ranged from 0.71 for the feasibility scale in Myanmar to 0.95 for the appropriateness scale in Myanmar). In Kurdistan, organizational level scales all showed adequate internal consistency reliability. At the consumer level, the acceptability and penetration scales showed adequate internal consistency reliabilities (α>0.70) in both sites. Psychometric properties of the organizational level scales in Myanmar and policy-level scales in both settings were not evaluated due to prohibitively small sample sizes.

Evaluation of construct validity showed that all scales at the provider level except the penetration scales were strongly positively correlated with the other implementation domains in both sites. Evidence to support the construct validity of scales at the consumer and organizational level was weaker.

Based on the instrument testing results in Kurdistan and Myanmar, the team has spent the past six months revising the measurement instruments and identifying new instruments that would add to the existing measures. Revision has been done based on the qualitative and quantitative results from the previous studies and in collaboration with experts in the field of implementation science. The resulting instruments are intended for use across different populations and settings and will be tested in Myanmar, the Ukraine and Zambia. The instruments have been developed based on the work with

mental health programs, but are intended to be adaptable for use in general health contexts in low and middle income countries.

We will translate this measure into Spanish and make any changes (as needed) for use in the Colombian context (although we expect no such changes may be needed). We will share lessons learned in using this measure in Latin America with the Myanmar team and other NIMH-funded hubs working in low- and middle-income countries.

Behavioral Health Integration in Medical Care Index (modified for Colombia). As described above, the Behavioral Health Integration in Medical Care Index (BHIMC) is an organizational measure of the level of behavioral health integration in medical practice settings. It evaluates policy, clinical practice and workforce dimensions of integration using mixed methods, i.e. combination of document review and observation. The BHIMC will be administered by a trained research staff member. The BHIMC has been adapted for use in Colombia, has been translated to Spanish, and has been described extensively in Section 6.3 above.

12.1.3 Cost of Implementing the Model of Care

The cost of providing mental health care within primary care settings in Latin America is not well characterized. It is critical to develop a better understanding of the costs of delivering mental health care in order to enable efficient and effective allocation of resources, including staff and medications, and to facilitate the integration of mental health care services into other primary care settings throughout Colombia, Latin America, and elsewhere. Measuring the costs of delivering the integrated model of mental health care in the current project will also be important for supporting the long-term sustainability of this model across diverse settings by allowing provider organizations to make informed decisions about staffing and budgeting.

It is important to note that measurement of the costs and resources used for delivering the proposed model of care are distinct from the price or fees for providing services or the reimbursement rates for different services. The costs of implementing the model of care are also distinct from the potential cost-benefit of providing mental health care integrated within primary care settings from the individual, payer, or societal level perspective.

The Time-driven Activity-based Costing (TDABC) Approach. The costs of implementing the proposed model of care for depression and alcohol use disorders will be measured using the time-driven activity based costing (TDABC) approach.[91, 92] The TDABC method of cost measurement involves creating a detailed process map to illustrate every administrative and clinical process activated during the treatment of depression and alcohol use disorders over a complete care cycle. The care cycle refers to the standard treatment course for patients seen at each clinic and typically begins with the moment that patients enter the clinic and continues through to the moment when they leave, and includes any necessary follow-up visits. The TDABC method will be used to determine the costs of the specific human, equipment, and facility resources used for delivering mental health care to patients as part of the model of care.

The TDABC approach will involve the following four steps:

STEP 1 ('Activities'): First, it is necessary to identify all of the activities, and the personnel who perform these activities, involved in providing treatment for depression and alcohol use disorders at

each of the clinic sites. This step will require shadowing patients and meeting clinical and administrative staff involved in the care process to determine how much time they spend on each of these activities. Process maps will be created to illustrate the flow of patients, to identify all activities involved in providing care, and to facilitate the remaining steps in the TDABC approach. Separate process maps will be generated for each of the participating clinical sites. A combination of shadowing, surveys of clinic staff, and interviews with staff and administrators will be used to determine the time in minutes required for each activity outlined in the care process.

STEP 2 ('People'): This step involves calculating the cost per unit of time for each of the personnel and equipment used throughout the various activities identified in Step 1. By determining the costs per unit of time, this step generates capacity cost rates. For example, to estimate the cost per minute for all the clinical and administrative staff involved in the care process, an individual's annual compensation will be divided by the total number of minutes per year that the person is available to work with patients. A combination of surveys and interviews will be used to gather these details.

STEP 3 ('Materials'): This step involves measuring the amount of materials, supplies, and medications that are consumed during the care processes identified in Step 1 and assigning costs to each of these items. Consumables can refer to any type of items that are used during the delivery of care, including latex gloves, test strips, or medications.

STEP 4 ('Facilities'): This final step involves determining the costs of things that are not directly consumed during the care process. For example, indirect costs such as the facility costs, electricity, building maintenance and cleaning, administrative costs, and health IT costs.

The TDABC approach enables providers to determine the costs of specific care pathways at the individual patient-level. This makes it possible to assess how costs potentially change based on the increasing complexity of patients' conditions (e.g., increasing age, multiple comorbidities, co-occurring substance use disorder), or as revisions are made to the delivery of care.

The TDABC approach can also make it possible to identify inefficiencies in the provision of care, and can inform efforts to move staff to higher value activities in order to improve outcomes for patients. For example, the TDABC approach can illustrate activities in the care process that could be performed by lower-paid staff instead of highly trained and expensive nurses or physicians, thereby enabling the more costly personnel to perform more complex clinical duties. This is especially important in settings where highly trained personnel such as nurses and physicians are in limited supply. Though efforts are necessary to ensure that any tasks that are shifted to different personnel will be performed at the same or higher level of quality.

The TDABC approach has been used in several clinical settings in the United States and in Europe, and has contributed to significant improvement in the efficiency and effectiveness of care delivery for patients with diverse medical conditions. Through improved resource allocation, the TDABC approach can identify opportunities in the delivery of care to improve value for patients by providing more effective care for each unit of cost. For example, in the current study, the TDABC approach may demonstrate that the proposed model of integrated care for depression and alcohol use disorders contributes to increases in costs. However, by linking cost measurement to patients' clinical outcomes, it may be possible to demonstrate that the added costs contribute to better outcomes and improved value for patients.

Timeline for TDABC Measurement. The TDABC measure will be collected before implementation of the integrated model of care in order to obtain an initial assessment of the costs of providing primary care at each of the study sites. This initial measurement using the TDABC approach will be essential in order to fully document use of staff, equipment, and facility resources within each clinical setting. The TDABC measure will then be collected following implementation of the care model (every year) to assess any changes in resource utilization. The TDABC approach will make it possible to capture changes in activities and associated costs following the implementation of the new model of care. All follow-up measurement using the TDABC approach will occur together with collection of the BHIMC tool.

TDABC Training. Training for using the TDABC approach will be provided to members of the research team and collaborators during a 2-day meeting to be held in Bogota in June 2017. This training will involve an overview of the procedures for accurately collecting data on resource utilization during patient visits using surveys and interviews. The training will also involve practicing this method at a demonstration site in Bogotá. The training will be conducted in a similar manner as the training for use of the BHIMC tool, and will contribute to ongoing project capacity building activities.

Other Cost Measures

Non-Study Medical and Other Services (NSMOS). We will include a measure associated with cost impact: Non-Study Medical and Other Services (NSOMS). The NSOMS assesses patients' medical resource use that is not part of the intervention, including non-treatment therapy visits, physician visits, residential and/or hospital detoxification, hospital and emergency department visits, and medication use through patient self-report. Through this effort, we will have a data collection instrument that can be applied in multiple settings. We will additionally assess cost per beneficiary data, as possible, using data from our partnering primary care sites. We have slightly modified this measure by removing sections that are not applicable to the primary care context in which we are working (ex: hospitalizations).

Non-Medical Expenses for Depression. This measure assesses the non-medical costs of depression.[93] This measure is in Spanish and has been used in Latin America and used by our team at Javeriana.

Additional Measures

Health and Work Performance Questionnaire (HPQ). This measure, developed by the World Health Organization, assess the impact of depression on work performance (including sickness absence, presenteeism, and critical incidents).[94] This measure is in Spanish and has been used in Latin America and used by our team at Javeriana.

Patient Outcomes. In addition to the patient measure for use in low and middle income countries described above, the primary patient outcome measure we will use to assess our hypothesized reduction in depression is the standardized Patient Health Questionnaire (PHQ-8).[95] We will assess problematic alcohol use (among the sample with problematic alcohol use) via the Quick Drinking Screen (QDS),[96] which is a 3-item questionnaire which asks about average drinking habits over the last ninety days. To assess functioning, we will use the 12-item World Health Organization Disability Assessment Schedule 2.0 (WHODAS)[97, 98] (to measure functional status and health-related quality of life).

Specifically, the WHODAS 2.0 assesses health-related difficulties across six different domains of functioning that are linked conceptually and operationally to the International Classification of Functioning, Disability and Health (ICF). The six major life domains are related to an individual's level of functioning and include: cognition (understanding and communication); mobility (ability to move and get around); self-care (ability to attend to personal hygiene, dressing and eating, and to live alone); getting along (ability to interact with other people); life activities (ability to carry out responsibilities at home, work and school); and participation in society (ability to engage in community, civil and recreational activities). The WHODAS 2.0 has shown good validity, internal consistency, test-retest reliability, and agreement with other measures of disability across many different settings and countries. The WHODAS 2.0 is also available in Spanish, and has been found to perform well across different cultures, among different subgroups, among people with physical disorders, and among people with mental health problems or addictions. Importantly, the WHODAS 2.0 has been used in several large clinical trials conducted in low-income and middle-income countries evaluating the integration of depression treatment or mental health care into primary care or other community settings, or treatment of alcohol use disorders in primary care settings.[99-102]

We will also assess anxiety among patients enrolled in this study. Anxiety is one of the most prevalent mental health conditions in Colombia.[107-109] According to the National Mental Health Survey (2015) the estimated lifetime prevalence of any anxiety disorder in adults between 18-44 years of age, and adults older than 45 years of age is 4.5% and 3.1% respectively.[109] Symptoms of anxiety frequently co-occur with depression and alcohol use disorders.[110, 111] Symptoms of anxiety are known to interfere with treatment for depression and alcohol use disorders, and negatively impact long-term treatment outcomes and illness course.[112] Given the high prevalence of anxiety disorders in Colombia, these symptoms likely interfere with treatment for other mental health conditions. Therefore, in the current study, it is critical to assess whether patients receiving treatment for depression or alcohol use disorders as part of the proposed model of care also experience symptoms of anxiety. It is important to ascertain whether the presence of anxiety may have an impact on treatment outcomes over time. We will use the General Anxiety Disorder screener (GAD-7), which is a 7-item self-reported screening questionnaire that has been validated to assess for generalized anxiety disorder (GAD) in outpatient and primary care settings.[113] The GAD-7 assesses seven items using a 0 to 3 scale. Screening and severity rating is based on the total score. The GAD-7 has been used to screen for anxiety disorders in primary care settings in low-income and middle-income countries[99], and among individuals exposed to violence and armed conflict in different regions of Colombia.[114]

Most patient measures will be assessed at baseline and every 3 months for a period of 12 months (for a total of 5 assessment timepoints per patient). The Integrated Measure of Implementation Context and Outcomes in Low and Middle Income Countries will not be administered to patients at baseline and will be administered at six month intervals instead of three month intervals, given the lack of sensitivity of the measure to change over short periods of time. The Health and Performance Questionnaire (HPQ) will be also be administered at 6 month instead of three month timepoints, given the length and patient burden of the measure. Although we will seek data from patients at these time intervals, data can be collected within 2 weeks before or after the targeted assessment date. Patients will be prompted by research and/or clinical staff when they are due to complete patient assessments. All measures will be offered to patients in Spanish.

COVID-19 Impact Outcomes. We will also assess the impact of COVID-19 among patients, providers, and administrators enrolled in this study currently or who have completed the study. Given the unknown and widespread implications of the COVID-19 pandemic in Colombia, it is critical to understand the context of COVID-19 for interpreting the study's findings. We will use the COVID-19

Impact Survey, which is a self-reported questionnaire developed by the NIMH U19 Scale-Up Hubs. The COVID-19 Impact Survey has been slightly modified from the version prepared by the NIMH U19 Scale-Up Hubs by removing subsections that do not assess the potential impact of COVID-19 (i.e., we removed the question "are you having thoughts of killing yourself right now" because, as worded, this question will not allow us to understand if responses are related to COVID-19), adding site-specific language (i.e., "since the lockdown in March 2020"), and adding follow-up items to clarify responses. The patient instrument consists of scales to measure Local Response to COVID-19 (1 item), COVID-19 Exposure (5 items), Impact of COVID-19 (19 items) and Access to Mental Health Services (10 items). The provider instrument consists of scales to measure Impact on Mental Health Services (8 items), Impact on Provider Burden and/or Burnout (3 items), and Impact on Experiences of Stigma (4 items). The administrator instrument consists of scales to measure Local Policy Response to COVID-19 (1 item) and Impact on Mental Health Services (6 items). The COVID-19 Impact Survey will be administered to patients already enrolled in the study at their follow-up visit(s) that occur every 3 months or to patients who have already completed the study at a separate scheduled visit after completion of the study. The COVID-19 Impact Survey will be administered to providers and administrators at their follow-up visit(s) that occur every 6 months or at separate scheduled visit(s). All measures will be offered to participants in Spanish.

12.2 Qualitative Outcome Measures

In addition to the quantitative outcome measures described above, we will also conduct interviews with partner setting administrators, clinical and administrative staff, and patients to evaluate the current state of treatment in Colombia and to help inform the model. These interviews will be conducted by our qualitative research team at Javeriana at 3- and 6-months post-implementation (+/- a 2 week window around the targeted data collection date). The goal of these interviews will be to evaluate stakeholder acceptance of the program and success of the dissemination strategies over the implementation period.

12.2.1. Administrative/provider Interviews

Administrative/provider interviews will assess implementation experiences, challenges to implementation and strategies used to facilitate implementation with different patient populations, changes made to workflow with use of the intervention, and salience of monitoring and feedback processes to inform providers and other stakeholders about the implementation success (approx. 5 at each site). We will also assess the extent to which patients initiated use of the program via inquiry of their providers after learning of the program through patient channels.

12.2.2. Patient Utilization Interviews/observations

Patient Utilization. We will recruit and follow a sample of patients (approx. 5 at each site) during the implementation project to explore feasibility issues regarding use, barriers and facilitating strategies for using the program, optimal dissemination strategies for promoting use of the program, and overall experiences using the program over time. These patient participants will be encouraged to document their experiences with the mental health service delivery model in an ongoing manner (e.g., note jotting, pictures, audio recording).

13.0 STATISTICAL DESIGN AND ANALYSES

13.1 Statistical Analyses.

Organizational implementation outcomes and patient-level implementation outcomes will be analyzed via linear mixed effects models (LMM) as is recommended for data from stepped wedge designs,[102] with the primary comparison being mean outcome before and after implementation of the novel care model. Each site will contribute observations both before and after implementation, and the model will include a fixed effect for time-period (to account for trends in outcome over time that are due to factors other than treatment implementation) and whether or not a time-period is before or after implementation. The primary hypothesis will be examined by testing if the coefficient of the pre- vs. post-implementation indicator term is different from zero. To account for potential correlation of observations within site, the model will include a random site effect; thus all statistical tests comparing outcomes pre- and post- implementation will take this within-site non-independence into account. LMMs use all available outcome data and allow for an unequal number of observations across sites and across participants per site.

Patient-level outcomes (evaluated longitudinally in participants from sites implementing the novel care model) will be evaluated via linear mixed effects models. These models will include fixed effects for time from enrollment to evaluate whether patient-level outcomes improve over time in sites implementing the novel care model. The models will also include a random site effect to account for similarities of outcomes of individuals within the same site, and random individual-level intercept and slope terms, to account for non-independence of repeated assessments within individual.

In addition to analyzing site-specific results (comparing sites before and after receiving the novel mental health service delivery model vs. the matched comparison site), we will aggregate data and conduct cross-site analyses to examine the extent to which patterns of results are similar/differ across populations and contexts. To integrate data across studies to explore patterns and generality of outcomes, we will use structural equation modeling (SEM)-based meta-analysis and meta-analytic SEM (MASEM)[115, 116]. MASEM is a type of path analyses synthesizing meta-analytic findings and it involves a two-stage approach: the first stage integrates data from several studies to produce pooled correlation or covariance matrices, and the second stage uses the pooled matrices as input data for inclusion in an SEM framework.

We will also document participants' mobile technology access/use in the study and examine how observed differences in access/use may relate to the perceived utility of the model as well as patient outcomes.

13.2 Rationale for Sample Size and Statistical Power

Sample Size. As we implement and evaluate our planned model of care across our collaborating 6 sites in accordance with our stepped wedge design, we expect a sample size of at least 1200 patient participants across this implementation project (sites that launch earlier will likely contribute more data and rural sites may contribute less data overall). These participants will contribute data to participant-level outcome variables (at 5 timepoints; enrollment, 3M, 6M, 9M, and 12M) and participant-level implementation outcomes (during the site evaluations every 6 months after implementation). Organizational implementation measures will be collected from providers and staff during 6-12 month intervals (both pre- and post-implementation) for a total of up to 6 intervals, with 10 providers and 10 staff members contributing data at each interval, and 25 patients contributing data during an interval for the IMICO and PSAT.

The modified stepped wedge design (6 sites, 2-6 time-periods, 10 observations per site per time-period) for the organizational implementation measures will yield 80% power at the two-sided 0.05 significance level to detect differences pre- vs. post-implementation that are at least 0.55-0.73 times a standard deviation.[102] This is a moderate-large standardized effect size. For the patient measures with 25 observations per site per time period, there will be 80% power at the two-sided 0.05 significance level to detect differences pre- vs. post- implementation that are at least 0.35-0.56 times a standard deviation. Because this is a modified stepped wedge design in that the number of assessment time-periods varies per site, we have based the power calculations on a full stepped wedge design with three and four time-periods, the average number of time-periods available per site.

The BHIMC and TDABC are collected once per site per time-period by research staff members. Assessment of change across time will be primarily used to evaluate qualitative changes pre- and post-implementation, but large effect sizes (1.78-2.4 standardized effect or greater) will be observed with 80% power at the two-sided 0.05 significance level. This sample size will allow us to detect the stability and replicability of cost savings among members within the target population. And, by recruiting about a portion of the sample from each of the partnering primary care systems, this sample size will allow us to demonstrate the feasibility and scalability of this model in multiple settings. Longitudinal analysis of patient-level outcomes post-implementation will include data from at least 1200 participants. At a sample size of at least 1200 (with, at least, two time-period measures per participant which is a highly conservative estimate of data collection), we will have at least 80% power at the two-sided 0.05 significance level to detect small pre- vs. post-implementation effect sizes 0.13-0.17.

13.3 Interim Analysis

We propose to conduct an interim analysis at the completion of the pilot project. We also propose to conduct an interim analysis half-way through the implementation study. This interim analysis will not include stopping rules for efficacy or futility. Instead, the results of these analyses will aid in modifying our implementation process, as needed, to better ensure sustainability. Formal efficacy evaluation will not take place until the completion of data collection.

13.4 Exploratory Analysis

We will additionally conduct exploratory moderator/mediator[117] analyses to examine how implementation context variables relate to implementation outcomes. A powerful approach to inference for indirect or mediated effects is bootstrapping. Bootstrapping[118] involves taking a random sample from the data with replacement numerous times and using the variability in the statistic from sample to sample to construct an interval estimate[119-121] conveying the direction, magnitude, and precision of an indirect effect. Indirect or mediated effect estimation that involves multiple mediators or lengthier causal chains is typically done in the context of a structural equation model[122] (SEM) or more recent extensions of SEM.[123, 124] Where current, adequate measures of mechanisms of action are unavailable, novel measures can be developed using confirmatory factor analysis[125] or item-response theory (IRT)[126] modeling. The two-stage approach to meta-analysis of structural equation models described by Cheung and Chan[115] can be used to synthesize indirect effects across a series of studies investigating similar interventions, mechanisms of action, and outcomes.

13.5 Missing Data and Dropouts

The number (%) of sites and patients with complete data will be reported. If scales have recommended methods for dealing with missing data, these will be applied. If scales do not have recommended missing data methods, multiple imputation will be used using 10 imputations and a fully conditional model based on Markov Chain Monte Carlo (MCMC). Once multiple imputations are conducted, the imputed data set will be analysed as a secondary analysis. Note that all quantitative data will be collected in REDCap. REDCap allows participants to skip questions they do not wish to answer. If a participant drops out before we collect all data, their collected data will still be used in analyses.

13.6 Demographic and Baseline Characteristics

Baseline demographic and clinical variables will be summarized for participants enrolled in the study. Descriptive summaries of the distribution of continuous baseline variables will be presented with percentiles (median, 25th and 75th percentiles), and with mean and standard deviation. Categorical variables will be summarized in terms of frequencies and percentages.

13.7 Safety Analysis

Adverse Events (AEs), including Serious Adverse Events (SAEs), will be presented as: (1) the number and proportion of participants experiencing at least one incidence of each event overall; and (2) the total number of each event overall in tabular form. Listings of SAEs will be sorted by system organ class (SOC), and preferred term (PT). Detail in these listings will include severity, relationship to study, and action taken, as available.

13.8 Incidental Findings

An issue of increasing importance in human participant research is that of "incidental findings." Incidental findings refer to observations of potential clinical significance unexpectedly discovered in research participants and unrelated to the purpose or variables of the study. If any research staff member and/or study clinician becomes aware of a potential incidental finding about a patient during the course of this study (e.g., patient may have undiagnosed symptoms of schizophrenia), this will be communicated to the clinical team at the primary care study site and the team will follow their standard clinical policies to appropriately assess the patient and provide/refer to care as needed.

14.0 INFRASTRUCTURE SUPPORT

14.1 Stakeholders

This partnership was launched via the support of the World Bank and includes a broad array of stakeholders, including academic organizations (Dartmouth College in the US; Pontificia Universidad Javeriana in Colombia; Universidad Peruana Cayetano in Peru; Pontificia Universidad Catolica in Chile), governmental organizations (Ministry of Health in Colombia; National Institute of Mental Health in Peru), as well as non-governmental and/or multilateral organizations (PAHO/WHO; The World Bank; industry partners; and primary care and regional hospital systems in Latin America).

We have expanded this broad group of stakeholders in Latin America in the proposed project to also include perspectives of non-profit patient advocacy organizations (Fundacion Internacional Unidos Contra la depression) and a public/private non-profit organization focused on quality decision-making in clinical practice and health policy (Instituto de Evaluación Technológica en Salud). We have additionally engaged large insurance companies in Colombia, which will be key to the sustainability of

this work. We have further engaged both US and Latin American-based research teams conducting implementation research that employs mobile health technology in several regions of Latin America (including Brazil, Guatemala, and Ecuador) (Dr. David Mohr at Northwestern University in Chicago and Dr. Paulo Rossi Menezes at the University of São Paulo in Brazil). This partnership will leverage the investment of NIMH in these collective activities to enable a new level of discovery and accomplishment across projects and offer the opportunity to accelerate the tempo and scientific achievement from this line of research. This partnership will also greatly enhance research capacity across Latin America. Overall, we have been fortunate to assemble an outstanding and broad team of collaborators and stakeholders which greatly enhances our ability to achieve the goals of the proposed project. These partnerships will also ensure that the study design is responsive to local needs, resources and expertise and enables synergies beyond what can be achieved through a traditional research study.

14.2 Project Launch and Annual Team Meetings

In the first quarter of Year 1, the project leadership held a planning meeting at Dartmouth (June 2016) and then we met in person with our entire team of stakeholders in Bogotá, Colombia for the initial project planning and project launch (September 2016). This face to face meeting with all stakeholders will then be repeated annually.

14.3 Administrative Meetings

The Administrative Team holds weekly meetings with both the Director's office and research team for ongoing communication and study management.

14.4 Learning Collaborative Meetings

Learning Collaborative sessions will be held quarterly by webinar and share lessons learned – including successes and challenges in implementation. These meetings will be in addition to the once per year in-person meeting in which these individuals will participate. Data collected at each site will be aggregated by site for review and discussion at this quarterly meeting. Quarterly meetings of this learning community will be co-led by Multiple PI Gómez and Consultant Uribe. This will allow for a rich sharing of information -- both from the discussions of collaborative participants as well as the rich systematically-collected dataset – which are key to refining and expanding science-based implementation efforts over time.

14.5 Research Capacity-building Meetings

This collaboration will entail quarterly "Research Capacity Building meetings" of the full Research Team, Consultants, Governmental, Non-Governmental and Multilateral Organizations, and NIH Project Scientists led quarterly by the Director's Office with all project personnel to discuss progress within each site, opportunities for increased cross-site collaboration/learning and areas where resources could be more efficiently shared, needs/progress of investigative teams, emerging trends in the field, priorities of the work, and training opportunities to address educational gaps/interests. Additionally a key part of this discussion will focus on shared learning and research capacity building across other parts of Latin America (Brazil, Ecuador, Guatemala) where Drs. Mohr and Menezes are conducting NIMH-funded research on scaling-up evidence-based mental health care.

14.6 Annual NIH Meetings

Core members of the project team will participate in annual NIH meetings to share lessons learned across NIMH-funded hubs.

14.7 Partnership and Advisory Board Meetings

We have engaged a governmental/multilateral organization advisory board in Latin America [including members of PAHO/WHO, the Ministry of Health in Colombia, the Ministry of Communication and Information Technology in Colombia] intended to ensure the intervention model is grounded in mental health policy and that the resulting data and lessons learned from the project inform the evolution of mental health policy over time across Latin America.

Organizations within this advisory board will be represented at in-person meetings of the entire project team (including research, governmental, payer, and non-governmental and multilateral organization partners) to be held in Bogotá, Colombia. They will be asked to review and discuss implementation research experiences and outcomes during the project and advise of their relevance to mental health policy. They will also be asked to communicate to this broad group of stakeholders the nature and evolution of mental health policy in Latin America over the life of the project.

15.0 REGULATORY COMPLIANCE AND SAFETY

15.1 Regulatory Compliance

This study will be conducted in accordance with the current version of the protocol, in accordance with the ethical principles outlined in the Declaration of Helsinki, International Conference on Harmonization Good Clinical Practice (GCP) Guidelines, and all other applicable regulatory requirements. An Operations Manual will be provided as a reference guide and study quality assurance tool.

15.2 Statement of Compliance

This study will be conducted in compliance with the appropriate protocol, current Good Clinical Practice (GCP), the principles of the Declaration of Helsinki, and all other applicable regulatory requirements. Participating sites must obtain written approval of the study protocol, consent form, other supporting documents, and any advertising for participant recruitment from their local Institutional Review Board (IRB) in order to participate in the study. Prior to study initiation, the protocol and the informed consent documents will be reviewed and approved by an appropriate Ethics Review Committee (ERC) or IRB(s) and the NIMH DSMB. Any amendments to the protocol or consent materials must be approved before they are implemented. Annual progress reports and local Serious Adverse Event (SAE) reports will be submitted to each IRB, and the NIMH DSMB according to their usual procedures.

15.3 Institutional Review Board Approval

Prior to initiating the study, investigators will obtain written IRB approval to conduct the study from the Dartmouth College Committee for the Protection of Human Subjects (CPHS). Should changes to the study protocol become necessary, protocol amendments will be submitted in writing by the investigators for IRB approval prior to implementation. In addition, CPHS in collaboration with the Research Ethics Committee at Pontificia Universidad Javeriana will approve the study protocol, all consent forms, recruitment materials, and any materials given to the participant. Annual reports and progress reports will be submitted to the IRBs annually or at a frequency requested by each IRB so that continuous study approval is maintained without lapse. The lead investigator is responsible for maintaining in his research files copies of current IRB/IEC approval notice(s), IRB-approved consent document(s), including approval for all protocol modifications. These materials must be available at any time for audit.

15.4 Informed Consent

As detailed in Section 9.3., patients at the partnering study sites who meet all eligibility detailed in Section 9.1 will be provided with an informed consent form to participate in the study [See Consent sheet in Appendix]. We intend to ask participants to complete consent forms electronically within REDcap (with appropriate electronic backups).

Research assistants will routinely move between study sites to aid in the oversight of participant recruitment, study implementation, and participant assessments. However, because we do not expect that research assistants will necessarily be at a given site every time a patient may be identified as eligible to join the study, and because the ultimate goal of this project is to create sustainable models of implementation, our partnering clinical staff at each study site will be trained on providing the electronic informed consent form to eligible patients and discussing with the patient both the interventions being offered to patients as well as the study expectations. Each site will identify one or more staff to function in this capacity. Clinician training on these procedures will be included in the planned staff training activities on this model of mental health care described in Section 8.0. As part of this training, clinicians will be required to demonstrate mastery of the consent process via role-playing. And they will be observed periodically by research staff to ensure procedures are being implemented with fidelity. Specifically, clinicians will screen patients, identify eligible patients, discuss treatment options for the patient and offer the consent form to patients who express interest in accessing the study's therapeutic resources (e.g., the web/mobile intervention) and willingness to complete study assessments in accordance with the assessment timeline (every 3 months, as described in Section 12.0). Clinicians will offer to read aloud the content of the consent form to the patient. The study Principal Investigators will regularly review participant inclusionary information to ensure eligibility criteria are being met.

Consent Procedure. As part of the consent process, the clinician describing the consent process will discuss potential risks and benefits of participation. Risks to patients are minimal but include talking about/answering questions about sensitive topics (such as depression and alcohol use) that may be difficult or emotionally upsetting to patients. The clinician providing consent will also discuss how the staff are trained to handle/manage these risks. S/he will also provide information about confidentiality and the voluntariness of participation. The clinical site will document if patients sign consent to join this study (in their medical record or a case note).

Information on confidentiality will emphasize that no personal information will be associated with the data; all data will be assigned with a study identification number (ID), and only this ID will be used for the study assessments. The list of study IDs (along with all research data) will be kept in a password protected, encrypted database, which is only accessible to approved research staff. Individual identifying information will only be maintained in a separate encrypted database with passwords known only to the PIs and specific members of the research team. No identifying personal characteristics will be used in any publication or presentation. Information on voluntariness will emphasize that participation in the study is completely voluntary. It will be highlighted that patients retain the right to refuse answers to any questions that they do not feel comfortable with. Patients retain the right to withdraw from the study any point in time, and refusal to participate will have no negative effect on the health care the patient receives through the study sites or at any other health care institution. Patients will have the opportunity to carefully review the written consent form and ask questions regarding the study prior to signing the informed consent form. The consent forms will need to be electronically signed by the patient and the individual who will oversee the informed consent process. Patients will be provided with a hard copy of

the consent form and staff will document in the research record that participants received this copy. Depending on the patient's interest, results of the study will be shared once the study is completed.

Wherever necessary, the participant's family will be advised of the need for confidentiality so that the family understands the conditions under which information will be shared. In addition to this, the individual providing consent at a study site will reiterate confidentiality to family members if any family member would be present at screening or at any other outcome assessment. Note that adult patients in Colombia typically visit their primary care provider alone. However, in cases where patients may wish to have a family member present, it is typical to discuss medical matters in the presence of family members. In these circumstances where patients may wish to have a family member present during the visit, their primary care provider will make an effort to confirm with the patient in private that their wish is to have their family member present. This approach is intended to ensure that the patient's wishes are respected, and is standard practice within primary care settings in Colombia.

While obtaining the consent, the patient will be explicitly informed that any incidence of violence (e.g., expressed intent to physically harm another person; see consent) required by law to be reported to authorities may be reported to the authorities without the consent of the patient. Furthermore, any clinical worsening (e.g. imminent risk of suicidal ideation) may result in referral for additional treatment and the research staff or clinicians could potentially disclose this information to treatment providers of the study or to family members. If a research staff member thinks a patient is at risk of harm to herself or to someone else, the research staff will report this to a physician/clinician at the study site without the consent of the patient. This information is also reflected in the informed consent form.

In addition to the above noted consent procedures, if an illiterate patient is eligible and wants to enter the study, the research assistant will read the informed consent form verbatim to the eligible participant. One impartial witness will be present during the reading and signing of the informed consent form to attest to the apparent understanding of the participant and their willingness to participate. If after listening to and fully understanding the informed consent form the patient wants to enter the study, the participant will use their thumbprint as a signature on the signature line of the informed consent form. Afterwards, the impartial witness will complete the information that accompanies the signature of the participant (PRINTED NAME and date) and the research staff will complete a note in the comments section of the informed consent, explaining the consent process for the participant. All of the procedures listed above that apply to literate participants will also apply to illiterate participants (i.e. they will be given opportunities to ask questions about any study procedures, will be provided with a hard copy of the informed consent for, etc.).

Patients who provide informed consent will then be asked to complete baseline participant assessments (described in section 12.0 of this protocol). Assessments will be delivered via a computerized assessment engine (REDcap) although paper versions of assessments and the informed consent form will be available if necessary (e.g., patient is uncomfortable completing computerized assessment or there are internet connection/technical difficulties). Any data collected onto paper assessments will be double-data entered into the REDCap database.

Additionally, provider and administrative staff at partnering primary care sites will all be offered the opportunity to complete the implementation context and outcome measure in this research project (including nurses, nursing assistants, social workers, health promoters, physicians and charge nurses,

program administrators). All participating staff will also be asked to provide consent to participate. Provider and administrative staff all need to be aged ≥ 18 years and have worked for the study site for at least 3 months. Research staff will provide informed consent to each staff member, who will be asked to sign an electronic consent in REDcap (along with the electronic signature of the research staff member who completed the informed consent process with staff). During a pause in face-to-face study activities due to safety concerns related to COVID-19, the research staff may mail informed consent documents for providers and administrative staff to sign and return by postal mail. Alternatively, study staff may provide participants the opportunity to provide informed consent signatures electronically through REDcap. In all cases, the study team will provide the phone number of the coordinator of each prospective participant's study site to allow each potential participant to voice questions or concerns prior to the provision of consent. We expect approximately 4-8 provider staff per site will complete the provider measure of implementation context and outcomes and about 2-5 administrator staff per site will complete the organizational level measure of implementation context and outcomes at each timepoint [See Consent sheet in Appendix].

A separate informed consent will also be sought for the sub-sample of patients as well as the subset of staff who are invited to participate in the qualitative study, as described in Section 12.2 [See Consent sheets in Appendix]. A qualitative research staff member will explain the purpose of the qualitative study to prospective participants and invite them to participate and ask for consent for the interview being recorded using a digital audio recorder. During a pause in face-to-face study activities due to safety concerns related to COVID-19, study staff may allow all participants in the qualitative study to provide informed consent by postal mail or electronically, through REDcap. The study team will provide the phone number of the coordinator of each prospective participant's study site to allow each potential participant to voice questions or concerns prior to provision of consent.

We will transcribe the audio recordings of the qualitative interviews to allow us to analyze this data. These transcriptions will not include information that could identify participants, and will be stored, along with the analog notes and audio recordings, in a locked facility in Javeriana University. We may use a translation service, such as google translate or a professional translation service, to translate the transcribed interviews into English. These translations will include no information that could identify participants and will also be stored in a locked facility in Javeriana University.

A separate informed consent will be sought for the currently enrolled patients, patients who have completed the study and are being re-contacted, providers, and administrators to participate in the COVID-19 Impact measure (which is being added as an additional study assessment), as described in Section 12.1. The IRB at Dartmouth and the IRB at Javeriana approved to waive a written consent from participants to complete the COVID-19 Impact measure as an additional study assessment due to COVID-19 related safety concerns. Instead, participants will be asked to provide verbal consent if they are willing to complete this additional assessment. In situations when it is not possible for in-person activities, the study team will obtain verbal consent through phone calls. During the conversation, a research staff member will provide information about the measure to participants by reading aloud a script verbatim, and invite them to participate, and ask them to give verbal consent. Whether the participant chooses to give consent or not will be documented for all invited participants. After the conversation, the study team will send a copy of the consent script via email, physical mail, or SMS to participants. For patients who already completed the study intervention, the study team will send a copy of the consent script via email or SMS and will serve as the final point of contact with our study.

We will recruit ethnically diverse adult patient participants from various states in Colombia in both rural and urban locations. All recruitment efforts will receive appropriate IRB approval.

15.5 Confidentiality

Confidentiality will be maintained in accordance with all applicable US federal regulations and/or state/Commonwealth law and regulations. Data will be maintained in confidence and such information will be divulged to the IRB, Ethical Review Committee, or similar expert committee; affiliated institution; and employees only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Participant records will be held confidential by the use of study codes, secure storage of any documents that have participant identifiers, and secure computing procedures for entering and transferring electronic data.

Study sites may be required by their institutions to obtain authorization from participants for use of protected health information. Sites will be responsible for communicating with their IRBs or Privacy Boards and obtaining the appropriate approvals or waivers to be in regulatory compliance. Releases of participant identifying information that are permitted by the HIPAA regulations (as applicable), but which are prohibited by other applicable federal regulations and/or state/Commonwealth law and regulation, are prohibited.

15.6 Investigator Assurances

Each study site must file (or have previously filed) a Federal Wide Assurance (FWA) with the DHHS Office for Human Research Protection setting forth the commitment of the organization to establish appropriate policies and procedures for the protection of human research subjects, with documentation sent to NIMH or its designee. Research covered by these regulations cannot proceed in any manner prior to NIMH receipt of certification that the research has been reviewed and approved by the IRB provided for in the assurance (45 CFR 46.103(b) and (f)). Prior to initiating the study, the principal investigator at each study site will sign a protocol signature page, providing assurances that the study will be performed according to the standards stipulated therein.

15.7 Financial Disclosure

All investigators will comply with the requirements of 42 CFR Part 50, Subpart F to ensure that the design, conduct, and reporting of the research will not be biased by any conflicting financial interest. Everyone with decision-making responsibilities regarding the protocol will confirm to the sponsor annually that they have met their institutional financial disclosure requirements.

A financial disclosure form and conflict of interest management plan has already been submitted to NIH from Dartmouth College for Dr. Marsch. Specifically, Principal Investigator Lisa Marsch, PhD is affiliated with Square2 Systems Inc., the business that developed the Square2® to be employed in the planned study. Dr. Marsch has worked extensively with her academic institution (Dartmouth College) to monitor the relationship between Square2 and her academic institution and ensure any potential conflict between her roles in each organization is appropriately managed. This Conflict of Interest management plan has also been submitted by Dartmouth College to the NIH. Additionally, all research staff who will work on this project will be informed of this relationship and provided with contact information of a third party whom they can contact if they should have any questions or concerns about this relationship. Further, the statisticians who will conduct all planned data analyses have no affiliation

with Square2 Systems, Inc. Dr. Marsch has successfully employed similar procedures in prior NIH-funded projects.

15.8 Clinical and Quality Monitoring

Procedures in Place to Ensure the Validity and Integrity of the Data. All research staff members involved in the collection of data will be well-trained on the administration of all assessments. They will have initially observed other trained staff members administering the assessments, will then be observed while they administer assessments and may also watch training videos on administering certain assessments when available. Additionally, completed assessments will be reviewed by our project Data Manager, and any errors detected in the administration of an assessment will be immediately brought to the attention of a study investigator and corrected.

Procedures to guarantee the accuracy and completeness of the data, during data collection, entry, transmission and analysis. Additionally, electronic tracking systems will be put into place to track when assessments are due for each participant and when they are completed. Any overdue assessments will be identified by a research staff member within the same week they are due (or sooner depending on the assessment), and the research staff responsible for administration of the assessment will be notified to immediately complete the assessment with the appropriate participant. Also, exhaustive contact information will be obtained for all participants, and updated regularly to help assure that we can successfully reach participants throughout the study and during follow-up. The Data Manager and statistician(s) will further review all data to ensure their accuracy (e.g., no data out of range, no alphanumeric data, etc.). We have successfully used similar procedures on other research projects.

Investigators will host periodic visits by the Dartmouth Project Manager to ensure study procedures are conducted appropriately and that study data are generated, documented and reported in compliance with the protocol, GCP, and applicable regulations. These monitors will audit, at mutually agreed upon times, regulatory documents, informed consent forms and corresponding source documents for each participant. Monitors will have the opportunity and ability to review any study-associated document or file.

Monitors will assess whether submitted data are accurate and in agreement with source documentation and will also review regulatory/essential documents such as correspondence with the IRB. Areas of particular concern will be participant informed consent forms, protocol adherence, reported safety events and corresponding assessments, and principal investigator oversight and involvement in the trial.

Qualified personnel at Javeriana (Quality Assurance or QA monitors) will provide site management for each site during the trial. QA staff will audit source documentation, including informed consent forms. This will take place as specified by the local protocol team, PI or lead team and will occur as often as needed to help prevent, detect, and correct problems at the study sites. QA personnel will verify that study procedures are properly followed and that site personnel are trained and able to conduct the protocol appropriately. If the QA personnel's review of study documentation indicates that additional training of site study personnel is needed, QA personnel will undertake or arrange for that training.

For all data, range and consistency checks will be performed at regular intervals separately for each data source and, where relevant, consistency checks will be carried out. Any queries identified will be resolved promptly by the data management team, and the database will be updated, maintaining the audit trial.

15.9 Inclusion of Women and Minorities

No Sex/Gender or Racial/Ethnic groups will be excluded. Based on patient data at our partner sites, we expect that approximately 65% of the participants will be women. And, we expect that approximately 60% will be white, 10% will be black, and 30% will be a mixture of other racial groups. We expect approximately 70% will be Hispanic.

15.10 Regulatory Files

The regulatory files should contain all required regulatory documents, study-specific documents, and all important communications. Regulatory files will be checked at each participating site for regulatory document compliance prior to study initiation, throughout the study, as well as at study closure.

15.11 Records Retention and Requirements

The regulatory files should contain all required regulatory documents, study-specific documents, and all important communications. Regulatory files will be checked at each participating site for regulatory document compliance prior to study initiation, throughout the study, as well as at study closure.

15.12 Reporting to Sponsor

The site principal investigator agrees to submit accurate, complete, legible and timely reports to the Sponsor (NIMH), as required. These include, but are not limited to, reports of any changes that significantly affect the conduct or outcome of the trial or increase risk to study participants. Adverse Event reporting and Serious Adverse Event reporting will occur as described below (section 15.16). At the completion of the trial, the Lead Investigator will provide a final report to the NIMH, as required.

15.13 Audits

The Sponsor (NIMH) has an obligation to ensure that this trial is conducted according to good research practice guidelines and may perform quality assurance audits for protocol compliance. The Lead Investigator and authorized research staff from Dartmouth, Javeriana, NIMH and other agencies such as the Department of Health and Human Services, the Office for Human Research Protection (OHRP) and the sites' Institutional Review Board may inspect research records for verification of data, compliance with federal guidelines on human participant research, and to assess participant safety.

15.14 Study Documentation

Study documentation includes all case report forms, workbooks, source documents, monitoring logs and appointment schedules, sponsor-investigator correspondence, and signed protocol and amendments, Ethics Review Committee or Institutional Review Committee correspondence and approved consent form and signed participant consent forms.

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study. Whenever possible, the original recording of an observation should be retained as the source document; however, a photocopy is acceptable provided that it is a clear, legible, and exact duplication of the original document.

15.15 Protocol Deviations

Any departure from procedures and requirements outlined in the protocol will be classified as either a major or minor protocol deviation. The difference between a major and minor protocol deviation has to do with the seriousness of the event and the corrective action required. A minor protocol deviation is considered an action (or inaction) that by itself is not likely to affect the scientific soundness of the investigation or seriously affect the safety, rights, or welfare of a study participant. Major protocol deviations are departures that may compromise the participant safety, participant rights, inclusion/exclusion criteria or the integrity of study data and could be cause for corrective actions if not rectified or prevented from re-occurrence. Sites will be responsible for developing corrective action

plans for both major and minor deviations as appropriate. Those corrective action plans may be reviewed/approved by the lead investigators with overall approval by the site's IRB. All protocol deviations will be monitored at each site for (1) significance, (2) frequency, and (3) impact on the study objectives, to ensure that site performance does not compromise the integrity of the trial.

Additionally, each site is responsible for reviewing their local IRB's definition of a protocol deviation or violation and understanding which events need to be reported. Sites must recognize that the IRB definition of a reportable event may differ and act accordingly in following all reporting requirements for both entities.

15.16 Safety Monitoring

Principal Investigators' Roles and Responsibilities for Data and Safety Monitoring. The Principal Investigators will assume primary responsibility for overseeing all data and safety monitoring functions to ensure the safety of participants in the research proposed within this application and to ensure the validity and integrity of the data obtained in these studies. The Principal Investigators will also regularly meet with the Co-Investigators and Consultants to track study progress and review these monitoring procedures. The investigative team will regularly oversee all aspects of the study, including participant recruitment, Informed Consent, data collection, data management and data analysis procedures, as well as regularly assess the risk/benefit ratio associated with participation in the study.

The investigative team will meet regularly (scheduled meetings once weekly) for the entire duration of the project.

Data and Safety Monitoring Board (DSMB)

An independent NIMH Data and Safety Monitoring Board (DSMB) will examine accumulating data to assure protection of participants' safety and data integrity throughout the duration of the study. The DSMB conducts established biannual reviews of accumulating safety and efficacy data (an additional reviews as indicated). It will determine whether there is support for continuation of the trial, or evidence that study procedures should be changed, or if the trial should be halted, for reasons relating to the safety of the study participants, the efficacy of the treatment under study, or inadequate trial performance (e.g., poor recruitment) or concerns about data integrity.

The study data will be reviewed by the NIMH Data and Safety Monitoring Board (DSMB) biannually. The DSMB will receive a data report from the study team on a schedule determined by the DSMB. The study team's submission to the DSMB is expected to follow the established reporting format developed in consultation with NIMH collaborator(s). The report will include the major variables necessary for monitoring safety and quality of data collection and integrity of the study, including subject enrollment and retention. The DSMB will also review the study protocol and consents before the onset of the study, and will review amendments to these documents. Based on this review, the DSMB has the authority to prevent the study to start or to stop the study after it has started.

The Principal Investigators will ensure all required DSMB reports are prepared, as required (as well as all required reporting to IRBs).

Adverse Events (AEs)

The Principal Investigators may appoint a Study Clinician (MD, PhD, or PI) for this study, who will review or provide consultation for each Adverse Event (AE) as needed. These reviews will include an assessment of whether the event was serious (Serious Adverse Event (SAE), whether the event was expected or unexpected, and the possible relatedness of the event to the study intervention or other study procedures. The Study Clinician will also provide advice for decisions to exclude, refer, or withdraw participants as required. This will include events that are serious, related and unexpected. The study staff will be trained to monitor for and report adverse events and Serious Adverse Events.

Definition of Adverse Events and Serious Adverse Events

An **adverse event** (AE) is any untoward or unfavorable medical occurrence in a human subject, whether or not considered study intervention related, which occurs during the conduct of a trial. An adverse event can therefore include high risk of suicide, threat of harm toward self or others, or clinical deterioration as defined by worsened physical or mental health.

Suspected adverse reaction is any adverse event for which there is a reasonable possibility that the study intervention caused the adverse event. A reasonable possibility implies that there is evidence that the study intervention caused the event.

Adverse reaction is any adverse event caused by the study intervention.

An **adverse event, suspected adverse reaction,** or **adverse reaction** is considered "**serious**" (i.e., a serious adverse event, serious suspected adverse reaction or serious adverse reaction) if, in the view of either the study medical clinician or sponsor, it:

1) Results in death: A death occurring during the study or which comes to the attention of the study staff during the protocol-defined follow-up period, whether or not considered caused by the study intervention, must be reported.

2) Is life-threatening: Life-threatening means that the study participant was, in the opinion of the medical clinician or sponsor, at immediate risk of death from the reaction as it occurred and required immediate intervention. Suicide attempts will be automatically classified as an SAE, given that they are life-threating.

3) Requires inpatient hospitalization or prolongation of existing hospitalization.

4) Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.

5) Is a congenital abnormality or birth defect.

6) Important medical event that may not result in one of the above outcomes, but may jeopardize the health of the study participant or require medical or surgical intervention to prevent one of the outcomes listed in the above definition of serious event. This may include threat of harm toward self or others.

Definition of Expectedness

Any adverse event is considered "unexpected" if it is not consistent with the natural course of the mental health problems under study in this project. Therefore, an "unexpected event" is any event non-consistent with the natural course of depression or alcohol use disorder (for example, a stroke that is unrelated to either of these conditions).

An "expected event" could include depressive symptoms, including suicidal ideation or attempt, heavy drinking, including hospitalizations due to heaving drinking, and other associated medical conditions).

Site's Role in Assessing Severity and Causality of Adverse Events

Appropriately qualified and trained study personnel will conduct an initial assessment of seriousness, severity, and causality when eliciting participant reporting of adverse events. A study medical clinician will review reportable AEs for seriousness, severity, and causality on at least a weekly basis.

Each of the sites has established practices for managing medical and psychiatric emergencies, and the study staff will continue to utilize these procedures. Treatment providers at each site will be responsible for monitoring participants for possible clinical deterioration or other problems, and for implementing appropriate courses of action.

The Principal Investigators will train all project staff to recognize and report any adverse event immediately to them. An adverse event involving human subjects can include high risk of suicide, threat of harm toward self or others, or clinical deterioration as defined by worsened physical or mental health. Other adverse events may also include the inadvertent disclosure by research staff of confidential research information to other persons and/or to staff of criminal justice or government agencies.

Guidelines for Assessing Severity

The severity of an adverse event refers to the intensity of the event:

Grade 1	Mild	Transient or mild discomfort (typically < 48 hours), no or minimal medical intervention/therapy required, hospitalization not necessary (non-prescription or single-use prescription therapy may be employed to relieve symptoms)
Grade 2	Moderate	Mild to moderate limitation in activity some assistance may be needed; no or minimal intervention/therapy required, hospitalization possible.
Grade 3	Severe	Marked limitation in activity, some assistance usually required; medical intervention/ therapy required hospitalization possible.

Guidelines for Determining Causality

The study medical clinician will use the following question when assessing causality of an adverse event to study intervention where an affirmative answer designates the event as a suspected adverse reaction:

Is there a reasonable possibility that the study intervention caused the event?

An example of an adverse event caused by the study intervention could be: a participant had a panic attack caused by their use of the application.

* *We are defining study participation as starting when a patient becomes a study participant, so the individual (patient or provider) in question would need to have consented and enrolled in the study. This means that screening is not included as "study participation*."

In the event such adverse events are reported to the Principal Investigators, they will immediately communicate the event to the appropriate institutional official at the institutional review board (IRB) followed by a written report in accordance with the timeline outlined in the table below. The institutional official with the IRB will then make a decision whether the reported event is a Serious Adverse Event (SAE) that must be reported to the appropriate Federal Agency. A SAE may include: death, a life-threatening event, hospitalization, an incapacitating event, all congenital abnormalities or birth defects among research subjects, or an medical event that may not result in one of the above outcomes, but may jeopardize the health of the study participant or require medical or surgical intervention to prevent one of the outcomes listed in the above definition of serious event. If necessary, the event will first be reported to the Federal Agency by telephone followed by a written report within three days.

A summary of reportable events, including their associated reporting requirements, is provided in the table below:

Reportable Event	**When is Event Reported to:**	**Reported By**
IRB/DSMB Suspensions or Terminations	**Research activities will be stopped immediately. Any suspension or termination of approval will include a statement of the reason(s) for the action and will be reported to** **NIMH DSMB/NIMH PO: within 3 business days of receipt.** **IRBs (Dartmouth and corresponding in-country): within 3 business days of receipt**	**Principal Investigator**
Death of a participant	**NIMH DSMB/NIMH PO: within 5 business days of the Principal Investigator first learning of the death** **IRBs: within 1 business day of the Principal Investigator first learning of the death.**	**Principal Investigator**
Unexpected Serious Adverse Events related to the study participation (except death for which see above)	**NIMH DSMB/NIMH PO: within 5 business days of the study team becoming aware of the SAE** **IRBs: within 5 business days of the study team becoming aware of the SAE**	**Principal Investigator**
Unanticipated Problems Involving Risks to Subjects or Others	**NIMH DSMB/NIMH PO: within 10 business days of the investigator learning of the event** **IRBs: within 10 business days of the investigator learning of the event**	**Principal Investigator**
Serious or Continuing Noncompliance with study protocol and human subjects regulations	**NIMH DSMB/NIMH PO: within 10 business days** **IRBs: within 10 business days**	**Principal investigator/Institution**
AEs that are deemed expected and/or unrelated to the study	**NIMH DSMB/NIMH PO: in the annual data report** **IRBs: at the time of continuing review**	**Principal Investigator**
SAEs that are deemed expected and/or unrelated to the study	**NIMH DSMB/NIMH PO : in the bi-annual data report**	**Principal Investigator**

	IRBs: at the time of continuing review	
Protocol deviations: **- Major (also known as protocol violations)** **-Minor**	**NIMH DSMB/NIMH PO: within 10 business days** **IRBs: within 10 business days** **NIMH DSMB/NIMH PO: in the annual data report** **IRBs: within continuing review**	**Principal Investigator**

Trial Stopping Rules. There are no a priori stopping rules in this study. As previously described, the Principal Investigators will oversee all data and safety monitoring functions to ensure the safety of participants in this research project and to ensure the validity and integrity of the data obtained in these studies. The Principal Investigators will also regularly meet with Co-investigators and Consultants to track study progress and review these monitoring procedures. If at any point the investigative team determines that the risk of a given participant continuing in the study is greater than the benefit of participating, this individual's participation will be discontinued and referred elsewhere as appropriate. This participants' study data will still be included in statistical analyses. If there is evidence that the risk to participants in general is greater than the benefits to them, this team will halt the trial and appropriate action will be taken (e.g., protocol revised, participants referred elsewhere as appropriate).

16.0 POTENTIAL RISKS AND PROTECTIONS AGAINST RISK

Potential Risks: The potential risks associated with the data collected are low for both patients and staff.

Risks from assessments and Laddr intervention: The types of data we plan to collect from both patients and staff (assessment, self-report questionnaires) will not harm the subjects' financial standing, employment, employability, or reputation, or expose the subject to civil or criminal liability. The types of risk associated with the data collected include possible fatigue, frustration, or the discussion of sensitive or personal information. If participants do not wish to answer any questions, they may elect not to do so, and may continue in the remainder of the study without penalty.

Patient participants may also feel uncomfortable reporting on their mental health. Additionally, participants may be concerned about confidentiality risk when using the Internet to access Laddr®, even on secured, encrypted connections. They may also be worried about prompts they receive on a mobile device designed to remind them to engage with the mobile intervention.

Participants may also find that some of the topics that Laddr addresses, including depression and/or alcohol use, may be sensitive topics. And they may be uncomfortable with some of this content. It is also possible they may find that this content does not help them.

Risks from electronic databases: There may be risks to subjects by virtue of their representation in electronic databases, principally involving the risk that privacy or confidentiality might be compromised if there were lapses in security of the information contained in these databases.

Protection against risks from assessments and Laddr intervention: To protect against the possible risks associated with participant assessments, which are fatigue and frustration, it will be made clear to participants, both during the informed consent process that they are free to discontinue their participation at any point without penalty. Any participant that experiences significant discomfort during assessment will be able to discontinue participation.

To protect against concerns that others may see when a participant receives a prompt from the Laddr system, the content of the prompts sent will be intentionally vague. While they will be designed to be meaningful to individual participants, they will not include specific references to study participation. Any participant that experiences significant discomfort during use of Laddr will be able to discontinue participation. If a participant has any concerns at any time during this study, or if they experience any worsening of symptoms or an adverse event due to use of the Laddr mobile intervention, this participant can discontinue participation and they can contact their doctor and the research directors for this study, Dr. Sergio Castro, at 320-8320 ext. 2812 or by email at sergiomariocastro@gmail.com and/or Dr. Magda Cepeda at 57-301-362-1356 or by email at mccepedag@gmail.com.

Protection against risks from electronic databases: To protect the privacy or confidentiality of subjects' data stored in electronic databases, every effort will be made to safeguard the confidentiality of research records, using data files free of information enabling individual identification of subjects, lock-and-key access to paper records, and computer data files maintained with encryption, password protection, and behind firewalls. We will remove individual identifying information from data representations so that security failures would not put individual privacy and confidentiality at risk. Individual identifying information will only be maintained in a separate encrypted database with passwords known only to the PIs and specific members of the research team.

We plan for the assessment batteries/tasks and resulting data to be available and coordinated through REDCap (Research Electronic Data Capture). Participants' completion of assessments will be completed via an encrypted Internet connection via 128-bit Secure Sockets Layer (SLL) - the standard technology for securing eCommerce and eBanking transactions on the Internet.

We will maintain Dartmouth IRB approval as well as IRB approval from Pontificia Universidad Javeriana and our study sites, as needed. Our data management expert at Dartmouth (Mary Ann Greene) can serve as an expert advisor on data management systems broadly and REDCap specifically.

All usage data provided by participants when using the web-based Laddr® intervention will be stored on a secure server behind 2 firewalls and will not be accessible to anyone not affiliated with the research project. Note that this mobile program will not collect data from participants about their suidical ideation or intent to self-harm. This mobile system will track how often participants use the mobile system which will aid the research team in understanding participants' usage of/engagement with the mobile intervention. Also, all data stored on these servers will be coded by participant ID number and encrypted for security purposes using SLL. All of these data will also be transferred via an encrypted Internet connection to the Dartmouth REDCap site.

While none of the procedures are associated with significant medical risk, we have plans for medical emergencies should they occur. Emergency telephone numbers and procedures are posted next to telephones in the primary care patient rooms. In addition, primary care partners will be required to establish (if they don't already have) a protocol for handling patients who communicate suicidal intent at any point during their participation.

17.0 ANTICIPATED BENEFIT

17.1 Potential Benefits of the Proposed Research to Human Subjects and Others

Participants will be receiving a web-based mental health intervention, they may benefit from a psychosocial intevention that may help them reduce health risk behavior. Healthcare systems will be receiving training and resources to embed science-based mental health care into primary care.

17.2 Importance of the Knowledge to be Gained

Overall, this project will create new knowledge to inform unprecedented, science-based approaches to scaling-up mental health implementation research and building sustainable research capacity and science-based policies and programs in Latin America. This project brings together an outstanding expert team to test and refine an entirely new model for delivering widespread, science-based, mental health care in Latin America. If successful, this approach can be expanded over time to embrace other areas of mental health (e.g., severe mental illness), chronic disease management, as well as health promotion prevention interventions based on community needs and priorities in Latin America. This project may also serve as an important demonstration project to LMICs globally as they tackle the significant burden of mental health disorders and scale-up access to evidence-based models of mental health service delivery.

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19.0 APPENDIX

- Informed Consent to Participate in Implementation Study – Patient Form
- Informed Consent to Participate in Implementation Study – Staff Form
- Informed Consent to Participate in Qualitative Interviews – Patient Form
- Informed Consent to Participate in Qualitative Interviews – Staff Form
- Adverse Event/Serious Adverse Event (AE/SAE) Report Form