FULL PROTOCOL TITLE: Mobile Health to Monitor Risk for COVID-19 and Improve Mental Health during the Pandemic

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Table of Contents

1.0 Objectives

1.1 The proposed research is directly relevant to public health because it aims to target health disparities in access to behavioral health care during the COVID-19 pandemic among Black, Hispanic, and American Indian (BLAI) individuals via testing an adaptation of an established, initially validated, low-cost, mobile application ('app') designed to reduce ongoing mental health concerns among BLAI individuals with elevated anxiety and/or depressive symptoms (Easing Anxiety Sensitivity for Everyone [EASE] App). Using a precision medicine approach, EASE targets anxiety sensitivity, a transdiagnostic individual difference factor implicated in the etiology, maintenance, and progression of anxiety and depressive symptoms. EASE includes COVID-19 symptom monitoring, exposure management skills, and psychoeducation on COVID-19-related stress and the impact of stress on susceptibility to infection and disease progression; if successful, this study will provide evidence that the EASE app-based intervention can address the public health concerns of anxiety and depressive symptoms among BLAI during the COVID-19 crisis. **Aim 1.** To compare the effect of EASE with COVID-19 specific elements (n = 420) to a standard-of-care digital intervention with educational material covering stress reduction, and anxiety and depression symptom management and COVID-19 specific elements (n = 420). To evaluate the efficacy of the experimental intervention across each race/ethnic group. **Aim 2.** To identify the therapeutic mechanisms of EASE, including theoretically driven mediators (i.e., anxiety sensitivity, subsequent changes in COVID-19 related stress and fear) and moderators (i.e., perceived racial discrimination, social support, and socioeconomic status).

1.2 **H1:** Those assigned to EASE will show greater reductions in anxiety and depression symptoms, and greater reductions in functional impairment in daily responsibilities (e.g., work performance, household maintenance, and social interactions, and relationships) relative to the control group. **H2:** Effectiveness of EASE will be similar across racial/ethnic groups. **H3:** Intervention effects on study outcomes will be mediated by reductions in anxiety sensitivity and changes in COVID-19 related stress and fear. **H4:** Perceived discrimination (worse intervention outcomes), social support (better intervention outcomes), and socioeconomic status (SES; lower SES associated with worse outcomes) will be examined as potential moderators of the EASE effects.

2.0 Background

COVID-19 Racial/Ethnic Disparities. Significant racial/ethnic health disparities have emerged in the United States (US)[5] related to the novel 2019 SARS2-Coronavirus disease (COVID-19).[17] Black and Hispanic persons experience significantly higher rates of COVID-19 relative to their proportion in the general population (19.9% and 31.4%, respectively),[18] and the rate of COVID-19 cases is 2.6 and 2.8 times higher among Black and Hispanic persons, respectively, relative to Non-Hispanic White (NLW) persons.[19] American Indian persons are 2.8 times more likely to contract COVID-19 relative to NLW individuals[19] and are approximately 5.2 times more likely to be hospitalized from COVID-19 relative to NLW persons.[5,8] Similarly, Black and Hispanic individuals are 4.7 times more likely to be hospitalized[20] relative to NLW persons. Indeed, proportionate prevalence rates of COVID-19-related hospitalizations are highest among American Indian, Black, and Hispanic persons and lowest among

NLW populations.[20] Death from COVID-19 is 2.1 times higher among Black, 1.1 times higher among Hispanic, and 1.4 times higher among American Indian relative to NLW individuals.[19] These data highlight the disproportionate, over-representation of BLAI individuals in COVID-19 infection rates, hospitalizations, and death relative to NLW individuals. Preexisting inequities related to social determinants of health and the effects of racism have likely contributed to these disparities.[21]

BLAI individuals are more likely to be affected by COVID-19-related stress relative to NLW persons.[9,10,22] Current rates estimate that 42.6% of Black and 46.3% of Hispanic individuals reported symptoms of an anxiety or depressive disorder between July 16-21, 2020.[7] These estimates are in stark contrast to the estimated 11.3% of Black and 10.3% of Hispanic individuals who reported symptoms of an anxiety or depressive disorder from January - July 2019.[23] Although NLW individuals experience comparable, albeit slightly lower, rates of anxiety or depression (38.8%), the racial/ethnic disparity gap for mental health outcomes is widening. To illustrate, data from 2019 found 0.2-1.2% difference in elevated anxiety or depressive symptoms between NLW and Black and Hispanic persons, with NLW individuals evincing a higher prevalence rate (11.5%).[23] The inverse pattern is now true with Black and Hispanic persons reporting higher rates of these symptoms by 4-8 percentage points.[7, 23] These data offer valuable insight into the potential mental health disparities that are developing from the pandemic. Additionally, although post-pandemic onset mental health data for American Indians in the US is lacking, American Indian community leaders have expressed continued concern for the mental health of their constituents given their propensity for worse physical health outcomes if infected with COVID-19 and generally worse mental health outcomes, including high rates of substance use and suicide.[24,25] Further, BLAI populations have lower access to mental health treatments and are less likely to engage with mental health treatments,[12,26] which may compound the severity of emerging COVID-19-related mental health disparities.[9,10] The pandemic has revealed changing mental health symptom patterns between BLAI and NLW, and emerging COVID-19 disparities in mental health symptoms are likely to widen without proper early intervention tactics.

Chronic Stress and Health Disparities. Impediments to care for BLAI individuals (e.g., racism, discrimination, mistrust of medical providers) and social determinants of health that make BLAI communities vulnerable to worse health outcomes (e.g., housing, income, access to healthcare) are known factors for chronic stress. Stressors are events or conditions that threaten, or are perceived to threaten, psychobiological equilibrium.[27] From a psychophysiological perspective, stress activates the Hypothalamic-Pituitary-Adrenal (HPA) axis.[28] The HPA axis' main function is to regulate the stress response. Continued and prolonged stress may disturb the HPA axis to the extent that negative feedback mechanisms are disrupted and may contribute to poorer health outcomes.[29] This perspective is in line with the allostatic load theory, suggesting that continued stress can be associated with negative physical and mental health outcomes.[30] Notably, BLAI individuals are at increased risk for high stress levels and greater chronicity of stress relative to NLW individuals, which accounts for a substantial portion of racial/ethnic health disparities.[31,32] In the US, People of Color are more likely than NLW adults to report stress related to contracting COVID-19 (71% vs. 59%), accessing healthcare (59% vs. 46%), and meeting basic needs (61% vs. 47%).[33] Chronic or repeated activation of the HPA axis often corresponds to prolonged or seemingly inescapable stressors, such as the present pandemic.[34] As such, the additive effect of COVID-19-related disease and stress burden exerted on stress responses systems saturated with pre-existing chronic stress is likely to amount in worse short- and long-term mental health outcomes among BLAI communities.

COVID-19 Stress Burden and Mental Health. Exposure to COVID-19 stress likely influences the

development, or exacerbation, of psychological and neurobiological processes that confer vulnerability to multiple types of psychopathology, including anxiety and depression.[3,4] Anxiety and depression represent two of the most commonly experienced mental health conditions across race/ethnicity.[35] In the following section, we describe a central stress-based, transdiagnostic mechanism that may underlie the link between COVID-19 stress and psychopathology, particularly anxiety and depression.[36] Taking a transdiagnostic approach allows the identification of core psychological and neurobiological processes that underlie multiple forms of psychopathology.[37] COVID-19 stress burden (accumulated impact of stress) may have a particularly pernicious influence when it happens among persons already struggling with greater stress exposure and pre-existing psychopathology. Specifically, higher degrees of COVID-19 stress can influence patterns of social, emotional, and neurobiological development in ways that facilitate the rapid detection of potential threats,[38] and by extension, may increase risk for multiple forms of psychopathology.

Importance of Stress and Stress Reactivity. Adverse life events increases the risk of psychopathology, particularly disorders of emotion.[39-41] Indeed, alterations in stress- and threat-response systems may compromise emotion-and attention-regulatory systems.[42] These data have often been used to explain the heightened risk for behavioral and affective disorders following exposure to adverse stressors in life.[43,44] This transdiagnostic theoretical framework also is at the crux of the assertion that increased rates of emotional disorders are an inevitable consequence of the pandemic.[45] After repeated exposure, a threat processing system involving a rapid appraisal-response system develops that is capable of orchestrating rapid reactions with little processing.[46] Thus, individual differences in the tendency to be 'stress reactive' (i.e., appraise threat rapidly) provide a fertile theoretical and clinical basis for understanding the nature of COVID-19 stress on emotional disorders among BLAIs specifically (see A.4.b).

Anxiety Sensitivity. Research in affective science has identified anxiety sensitivity (AS) as an 'affect amplifier' because it represents a fundamental threat appraisal process.[47] Specifically, AS refers to the fear of anxiety symptoms, including bodily sensations, which results from beliefs about the harmful social, psychological, or physiological consequences of such symptoms.[48] AS has consistently been identified as a malleable risk factor for the onset of panic attacks, panic disorder, generalized anxiety, depression, and posttraumatic stress, in prospective studies of adults across race/ethnicity.[49-52] Specifically, AS has been found to predict the development of panic attacks and has been linked to panic-like symptoms, anxiety, fear, and clinical anxiety and depressive disorders across a range of diverse community and clinical samples.[52-56] It is important to note that AS predicts anxiety symptoms above and beyond trait anxiety, demonstrating the incremental validity of this construct.[52,57] AS also has demonstrated strong racial/ethnic invariance across a range of samples, including BLAI groups.[14,54,55,58] Individuals with high AS may be more likely to attend to bodily sensations that are associated with anxiety, such as respiratory symptoms, stomach distress, fatigue, and body aches, and to misinterpret these symptoms as dangerous or catastrophic.[59,60] These interpretations of bodily sensations can lead to increased anxiety and perpetuate a cycle of increased attention to and misinterpretation of bodily cues. This process may eventually lead to avoidance and increased symptoms of anxiety, stress, and depression, and it has the potential to exacerbate stress on the body systems, which, in turn further compromises the immune system and places individuals at risk.[61] This maladaptive cycle may be particularly relevant to BLAI populations during the pandemic given their increased likelihood of COVID-19 exposure, challenges with enacting behaviors to reduce the likelihood of infection, concerns about the increased likelihood of worse outcomes if infected, and

greater pandemic-related stress (e.g., job loss, income reduction, childcare needs). Further, because some BLAI populations experience psychological distress somatically,[62-64] AS is particularly relevant to these groups because it amplifies threat response to somatic perturbation.

AS Relevance for BLAI Individuals. AS is highly theoretically relevant to BLAI individuals based on several lines of work. First, BLAI individuals have increased awareness of the negative outcomes of physical symptoms and illnesses.[65-69] Second, BLAIs experience more somatic symptoms, and are more distressed by these symptoms compared to NLW persons. Third, BLAI individuals are more often diagnosed with comorbid psychiatric disorders than NLWs.[70-72] Finally, affective disturbances are associated with an increased prevalence of comorbid medical diseases, such as chronic pain, arthritis, and cardiovascular disease, and many of these chronic medical conditions disproportionately affect BLAIs.[73-75] Thus, interrelated lines of work suggest that BLAI populations may be more apt to react to interoceptive symptoms with heightened anxiety[76,77] and mood disturbances. Yet, past work has not leveraged the potential of AS to better address mental health inequalities in the context of the pandemic which represents a unique and unprecedented period that may contribute to increased mental health disparities.[78-81]

AS: Precision Medicine Treatment Target. Approaches to break the link between AS-anxiety/stress/depression have been developed and have demonstrated strong efficacy.[82-84] Indeed, AS is malleable in response to psychosocial intervention,[85] making it a prime mechanistic agent to target in prevention/intervention programs. Reductions in AS improve clinical outcomes among general clinical and nonclinical populations, highlighting the relevance of this construct within the general population.[85,86] AS reduction treatment can be distilled in as few as 1-4 treatment sessions both in-person or via computer, with equal success.[83,87,88] AS treatment decreases AS by providing psychoeducation about the true dangers of anxiety related bodily sensations; cognitive restructuring of catastrophic appraisals of anxiety related bodily sensations and life experiences; and by helping individuals develop greater tolerance to these sensations through interoceptive and in vivo exposure exercises. Such decreases, in turn, result in reduced anxiety, depression, and related conditions (e.g., stress burden).[89] Thus, a cognitive-behavioral approach that targets maladaptive cognitions about bodily symptoms (i.e., AS) may have significant clinical utility in decreasing anxiety and depressive symptoms in the context of COVID-19. Indeed, COVID-19 stress and associated beliefs for exposure and health-risk associated with COVID-19, which is likely to be elevated among BLAI persons, may motivate vigilance to internal sensations. COVID-19 may thus serve as a context in which individuals learn to fear bodily sensations because such sensations could potentially have harmful consequences.[90] Yet, intervention work to address the impact of AS on mental health outcomes among BLAI individuals has not been leveraged in the context of COVID-19 stress.

3.0 Inclusion and Exclusion Criteria

Table 1. Inclusion and Exclusion Criteria

Eligibility Criteria:	Exclusion Criteria:
1. ≥ 18 years of age 2. Self-identify as Black, Hispanic, American Indian, or NLW 3. Clinically significant anxiety and/or depressive symptoms as evinced by a score of 8 or higher on the Overall Anxiety Severity and Impairment Scale (OASIS)[122] and/or Overall Depression Severity and Impairment Scale (ODSIS)[123] 4. Reside in the United States	1. Not fluent in English 2. Lifetime or significant cognitive impairment

5. Willing/able to complete EMAs on study provided or personal smartphone for 6-month study period 6. Willing and able to complete the 3- and 6-month follow-up assessments via Insight™ app and over the phone (i.e., qualitative interview) 7. Score ≥ 4 on the REALM-SF indicating > 6th grade English literacy level (needed to complete EMAs)	4. Identifying as a race/ethnicity for which the corresponding study cell has been filled

Participants will be recruited online via social media and internet outlet (e.g. Craigslist, Facebook) advertisements that target residents of the United States. Individuals who click our ads will read the study description and complete a brief study screener in REDCap. Further, we will utilize Qualtrics Panels Recruitment as a method of recruiting new participants. Qualtrics will reach out to individuals who express interest in participating in order to determine eligibility of recruited individuals, Qualtrics will have access to identifiable information to include the following: (1) Full name, (2) Phone number, (3) Phone number (secondary), (4) Email address, (5) Age, (6) Date of birth, (7) Ethnicity, (8) Race, (9) Gender assigned at birth. The Qualtrics survey will also utilize the Overall Anxiety Severity and Impairment Scale and the Overall Depression Severity and Impairment Scale. Additionally, we will be recruiting participants using university and online LISTSERV services. Also, we will be recruiting American Indian participants through BuildClinical.BuildClinical will direct individuals to their own platform where they will receive more information about the study. They will also be able to take our pre-screener survey through BuildClinical and we will be able to download a list of pre-eligible participants. This program will have access to the following information: (1) Full name, (2) Phone number, (3) Phone number (secondary), (4) Email address, (5) Age, (6) Date of birth, (7) Ethnicity, (8) Race, and (9) Gender assigned at birth. BuildClinical will create all recruitment materials for use on their platform once recruitment through BuildClinical is approved by the University of Houston Institutional Review Board.Those who initially meet the study inclusion criteria will complete a phone call with study staff after completing the REDCap screener. During this call, study staff will verify that individuals meet the study inclusion criteria.

The REDCap screener will include assessment of demographics, anxiety (OASIS), depression (ODSIS), and state of current residency. Demographic-Treatment History Questionnaire will assess sex, age, race and ethnicity, occupation, and current monthly income. The OASIS is a 5-item measure that has demonstrated strong psychometric properties to identify those with clinically significant anxiety. The ODSIS is a 5-item measure that has demonstrated strong psychometric properties to identify those with clinically-significant depression. Potentially eligible participants will be asked to upload a picture to confirm their identity (such as a photo ID). If their identification photo information does not fully match (e.g. last name change), the participant can provide a secondary form of identification to confirm their identity. At the phone screener, a trained research assistant will obtain informed consent, confirm the state of residency by requesting participant address and current location, assess literacy, evaluate cognitive impairment using the **Six Item Cognitive Impairment Test (6CIT)**, and assess English literacy. The trained research assistant will also obtain U.S. residency status, date of birth, and social security number. To be in compliance with IRS regulations, the University of Oklahoma must collect residency status for all participants and all payments are required to be reported as outlined in this policy. Further, participant name, tax identification number (SSN or ITIN), address, amount paid and source of funding for the payment will be collected. The full participant payment policy for the Oklahoma University Health Sciences Center can be found here: https://www.ouhsc.edu/policy/#19931991-section-557---participant-payment-policy. We would like to stress that U.S. citizens, Permanent Residents, Resident Aliens, and Non-Resident

Aliens will receive equal compensation for their participation. Per the Oklahoma Taxpayer and Citizen Protection Act of 2007, undocumented immigrants are prohibited from receiving payment, and thus will be excluded from this study. The informed consent procedure will be completed by phone and REDCap (i.e., participants will use REDCap to review the informed consent document along with research staff, REDCap will be used to obtain signatures). The REALM-SF[138] will be employed to assess literacy.

Economically disadvantaged persons will be included in the study as research suggests that a significant portion of BLAI individuals are low income.

None of the following populations will be specifically recruited:

- Adults unable to consent
- Individuals who are not yet adults (infants, children, teenagers)
- Pregnant women
- Prisoners
- Students for whom you have direct access to/influence on grades

4.0 Vulnerable Populations

N/A

5.0 Number of Subjects

STUDY-WIDE: Taking failed screeners and participant attrition into account, we expect to consent 1300 participants. We anticipate randomizing a total of 880 participants (N = 880; 220 Black, 220 Hispanic, 220 American Indian, and 220 NLW; Intervention group, n=440, control group, n=440).

6.0 Recruitment Methods

STUDY WIDE:

Participants will be recruited online via social media and internet outlet (e.g. Craigslist, Facebook) advertisements that target residents of the United States. Individuals who click our ads will read the study description and complete a brief study screener in REDCap. We will also utilize university and online LISTSERV services to recruit participants, as well as Qualtrics Panels Recruitment to gather basic demographic information to assess primary eligibility. Also, we will be recruiting American Indian participants through BuildClinical. BuildClinical is a data-driven platform that helps academic researchers recruit participants for research studies more efficiently using social media, software, and machine learning.BuildClinical will direct individuals to their own platform where they will receive more information about the study. They will also be able to take our pre-screener survey through BuildClinical and we will be able to download a list of pre-eligible participants. This program will have access to the following information: (1) Full name, (2) Phone number, (3) Phone number (secondary), (4) Email address, (5) Age, (6) Date of birth, (7) Ethnicity, (8) Race, and (9) Gender assigned at birth. BuildClinical

does not interact with data outside of sending the data to the University of Houston. BuildClinical's Secure Socket Layer (SSL) software encrypts all inputted information and keeps the information private and compliance. BuildClinical will create all recruitment materials for use on their platform once recruitment through BuildClinical is approved by the University of Houston Institutional Review Board. Those who initially meet the study inclusion criteria will complete a phone call with study staff after completing the REDCap screener. During this call, study staff will verify that individuals meet the study inclusion criteria and staff will review study details with each individual. We will also post flyers in the community and around the UH and OU campuses as permitted (flyer attached). Additionally, we will recruit residents specifically from OK and TX through various media outlets (e.g. TV, Radio). Finally, we will utilize community organizations (e.g. Legacy Health, Lone Star clinic) for recruitment purposes as well.

7.0 Multi-Site Research Communication

To facilitate communication, we have budgeted for face-to-face meetings of the PIs and the larger team and will include site-specific investigators at each of the local meetings. We hold weekly lab meetings and monthly conference calls across sites for all investigators to review recruitment progress, assessment issues, and discuss publications. Other informal conferencing occurs between the PIs, who routinely speak at least weekly and much more frequently by electronic means. This organizational structure has been in place for the past 5 years and functions efficiently and without major difficulties. We have collaborated for many years and conflicts have not arisen. Should a conflict arise, Dr. Zvolensky has final say on administrative and fiscal issues, and on issues related to treatment development. Dr. Businelle has final say on issues related to his budget components (e.g., staffing) and issues related to technology development and adaptation. In the unlikely event that the PIs are unable to resolve an issue, it would be put forward for discussion with the investigative team and a vote would be taken among the 9 participants. Dr. Zvolensky and Businelle would accede to the voting results. In the unlikely event that the investigative team cannot resolve the issue, it will be referred to the Data Safety and Monitoring Board (DSMB) who will review the matter and determine an equitable and binding decision. The full DSMB plan is located on page 25 of the grant under the heading, "Data and Safety Monitoring Plan".

The UH study team, under the supervision of the contact PI, will provide services to:

- Coordinate communications with partnering sites
- Request and receive information and documentation from partnering sites
- Develop template materials for review by the UH IRB and for limited modification by participating sites
- Submit materials from all sites to the UH IRB and coordinate responses to any IRB queries
- Provide documentation to participating sites

Participating sites will follow local procedures to coordinate, collect and verify information such as:

- Local context
- Site variations in areas such as recruiting, informed consent, HIPAA, populations
- Conflict of Interest disclosure and management
- Completion of ancillary reviews

- Training and qualifications of study team
- Continuing Review or Closure information
- Reportable Events

The contact PI will maintain a copy of this communication plan and any other communication plans that are developed. Copies will be made available to the participating sites as appropriate.

Before initiating the study, each participating site will execute a reliance agreement with the IRB which will clarify the roles and responsibilities of the sIRB and the site.

The Insight app encrypts all data as it is collected. This data is synced with Azure servers up to four times per day. Study data are available through Insight's encrypted web portal (i.e., the content management system). Each individual member of the research team has a STRONG password. Only team members that require access to study data will be granted the ability download data directly to their encrypted university computer. Given both sites are able to download study data directly, there is not a need to transmit it across study sites. Research data will be encrypted and saved to the study phones or through REDCap.

As required by NIH, we will provide de-identified data from this project to interested individuals one year following achievement of the aims of the project (i.e., publication of the main outcome papers). These data will be provided in digital format (i.e., disk) with clear labels for all variables. Data will be de-identified and released directly by the investigators that provide evidence of their institutional IRB approval for planned analyses of the data. Our team will be available to address queries.

8.0 Study Timelines

The present study will include a baseline assessment, a 3-month intervention period, a 3-month continued assessment period (with access to intervention materials), and 3- and 6-month post-baseline assessments that includes a qualitative interview for selected participants via phone or online platform (e.g., Zoom). The qualitative interviews will be recorded and securely stored for qualitative analysis (or completed by the participant via REDCap survey if a medical condition prevents them from being able to speak for long periods of time). Recordings will be transcribed by internal staff, Microsoft Transcribe, or by approved contractors. When using Microsoft Transcribe, all transcriptions will be reviewed by study staff. Hence, the total duration of an individual subject's participation in the study will be 6 months. We expect each study appointment will take approximately 30-60 minutes to complete.

Baseline timeline: All study assessments as well as all EMAs will be conducted remotely through the Insight app. Participants who do not have a mobile phone will be mailed one. The Insight™ app will be downloaded and activated during the baseline session using a unique activation code provided by the research team. All interactions with the Insight and EASE app will be date, time, and Geolocation (GPS) stamped and app feature use will be recorded for future analysis. After downloading the Insight app, participants will use the app to complete the baseline assessment. We expect participants will take approximately 30-minutes to complete all baseline assessment measures (please refer to section 10.0 procedures involved for a detailed list of measures participants will be prompted to complete). Following completion of the baseline assessment, the

app will request a code. This code will be used to ensure that the participant is placed in their randomly assigned study condition (EASE or Control). Upon entering this code, the app will automatically begin prompting twice daily EMAs for 6-months (please refer to section 10 below and Table 3 for a list of EMA assessments and more detailed information).

Follow-up timeline: Participants will complete follow-up assessments at 3- and 6-months following the baseline assessment, which will also be completed using the Insight app, in the same manner as the baseline assessment. Assessments to be conducted have been detailed below (please see 10.0 procedures involved). We expect the 3- and 6-month follow up assessment sessions will each take participants approximately 30 minutes to complete. Moreover, during the time between the baseline and 6-month follow-up assessments (6-month continuous assessment period) participants will continue to receive daily EMAs and will have access to all intervention materials included in the app.

Project Timeline. Year 1 will focus on obtaining IRB approval (i.e., submit application, respond to reviewers, and re-submit), hiring and training research staff, and beginning the enrollment. Year 2 will focus on recruitment, enrollment, and collecting follow-up data. Year 3 will focus on collecting follow-up data, data cleaning/analysis, and manuscript preparation and dissemination, including presenting findings at professional conferences and community-based events. For the present study, we expect approximately 50% of participants who click on our advertisement to be eligible; 75% of those who complete the phone screener to be eligible; and 95% of those to consent to participate. Weighted compensation schedule and reminder calls will be utilized to minimize subject dropout. Based on our ongoing work, we expect to enroll 39 participants each month, on average, across the 21-month enrollment period. We expect to retain 80-90% of subjects at each follow-up assessment points.

Project Timeline

ACTIVITIES TO BE COMPLETED	Year 1				Year 2				Year 3			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
HIRING AND TRAINING STAFF; STUDY PREPARATION	•											
IRB SUBMISSION AND APPROVAL	•											
ENROLLMENT AND ADMINISTER STUDY PROCEDURES		•	•	•	•	•	•	•	•	•		
DATA CLEANING										•	•	
DATA ANALYSIS & DISSEMINATION											•	•

Q1: Months 1-3, Q2: Months 4-6, Q3: Months 7-9, Q4: Months 10-12. *Study Implementation (Year 1)*: Staff hiring and training; IRB submission; and recruitment preparation. *Enrollment and Study Procedures (Years 1-3)*: Recruitment; screening; enrollment; assessment; and follow-up. *Data Cleaning and Dissemination (Years 3)*: Collect follow-up data; data cleaning and merging, analysis, and interpretation; research dissemination preparation; and manuscript preparation.

9.0 Study Endpoints

The primary study endpoint will be recruitment of all study subjects at the end of the study enrollment period. The secondary study endpoint will be the collection of study data from all participants following the 6-month follow-up.

10.0 Procedures Involved

All study data (both survey data and EMAs) will be collected through the Insight app which participants will be asked to download during their baseline assessment, with the only exception being the study screener, consent process, and qualitative follow-up interviews for selected participants which will be completed through REDCap and phone call. Qualitative interviews will

be recorded and transcribed for analysis. All data being collected from research participants will be input into the Insight app by participants themselves.

Participants will be recruited online via social media and internet outlet (e.g. Craigslist, Facebook) advertisements that target residents of the United States. Individuals who click our ads will read the study description and complete a brief study screener in REDCap. Participants will also be recruited through Qualtrics Panels Recruitment which will gather basic demographic information to assess eligibility. Also, we will be recruiting American Indian participants through BuildClinical. BuildClinical is a data-driven platform that helps academic researchers recruit participants for research studies more efficiently using social media, software, and machine learning.BuildClinical will direct individuals to their own platform where they will receive more information about the study. They will also be able to take our pre-screener survey through BuildClinical and we will be able to download a list of pre-eligible participants. This program will have access to the following information: (1) Full name, (2) Phone number, (3) Phone number (secondary), (4) Email address, (5) Age, (6) Date of birth, (7) Ethnicity, (8) Race, and (9) Gender assigned at birth. BuildClinical does not interact with data outside of sending the data to the University of Houston. BuildClinical's Secure Socket Layer (SSL) software encrypts all inputted information and keeps the information private and compliance. BuildClinical will create all recruitment materials for use on their platform once recruitment through BuildClinical is approved by the University of Houston Institutional Review Board. Additionally, participants will be recruited via university and online LISTSERV services. Those who initially meet the study inclusion criteria will complete a phone call with study staff within one week of completing the REDCap screener. During this call, study staff will verify that individuals meet the study inclusion criteria, staff will review study details with each individual; and interested individuals will complete the informed consent process (signatures will be collected digitally via REDCap) and begin the screening assessment. Participants who are found to be eligible during the screening process will then be instructed to download the INSIGHT app onto their smartphone to complete the Baseline assessment. If a participant requires a study phone, they will be mailed one and scheduled to complete the baseline assessment once the phone has been received. Participants who report they are not the only users of their phone will be mailed a study phone for the study.

Baseline assessment:
During the baseline assessment, all participants will be asked to download the Insight app. Upon downloading Insight, participants will be provided with a unique activation code which they will enter onto Insight to gain access to the Baseline assessment. Upon completion of the Baseline assessment, the app will request a second code that will be used to place participants in the correct group.

Though participants will be assigned to different mobile interventions, all participants will use the Insight app to answer the baseline, follow-up, and EMA surveys. We will be using the Insight app to collect all of the study data (with the exception of the study screener, consent, and qualitative interviews which will be obtained via phone call and REDCap). Below is a detailed list of all study measures which will be administered to participants during their baseline session, via the Insight app:

Baseline measures:
Sociodemographic variables will be assessed using a standard form we have used in many prior studies. SES will be measured as income and education.
AS will be assessed using the 5-item SSASI we developed, which has excellent psychometric properties. Research has supported using a cut-off score of 5 to identify moderate to high AS

individuals (reflecting top 1/3rd of distribution).
The Sheehan Disability Scale (SDS)[152] is a psychometrically sound, brief, 5-item self-report tool that assesses functional impairment in work/school, social life, and family life.[16]
The Social Support Questionnaire-Short Form (F-SozU K-6) List[141] is a well-validated 6-item measure of social support.
The PEG scale is ultra-brief 3-item measure derived from the brief pain inventory and validated in ambulatory care settings.[143] It demonstrates strong properties to detect change in pain.[153]
The Everyday Discrimination Scale[139] is a 6-item, validated measure of discrimination.
The Coronavirus Racial Bias Scale (CRBS)[140] is a 4-item Likert scale designed to assess disparities in COVID-19, including likelihood of contracting COVID-19, lack of appropriate healthcare, as well as negative social medial posts against certain racial groups.
The Fear of COVID-19[145] scale is a 6-item, validate measure to assess emotional fear and somatic expression of fear related to COVID-19.
The 4-item Perceived Stress Scale (PSS-4) is a 4-item global measure of perceived stress. The Patient Health Questionnaire (PHQ-4) is a 4-item measure that combines the two-item measure (PHQ–2), consisting of core criteria for depression, as well as a two-item measure for anxiety (GAD–2), both of which have independently been shown to be good brief screening tools. The Health-Related Quality of Life (HRQOL) is used to assess physical and mental health.
The MacArthur Scale of Subjective Social Status (MSSS) is a self-rating scale on which a person indicates where they believe they fall on a 10-rung ladder that represents the levels that a person may occupy within society. Two versions of the ladder will be included, one linked to traditional SES indicators (the SES ladder) and the second linked to standing in one's community (the community ladder).
The COVID 19 Vaccine Hesitancy Survey will measure hesitancy to take the COVID vaccine.
The Financial Strain Questionnaire (FSQ) includes 9-items rated on a scale from one to four that assess level of financial strain currently being experienced.
The Behavioral Risk Factor Surveillance System (BRFSS) Inadequate Sleep Questionnaire is a 5-item measure used to detect sleep problems that result in health burden. Frequency of Attendance at Religious Services is a two item measures that asks individuals to indicate the frequency of their attendance at religious services.
The Discrimination Burden measure contains 4-items that assess perceptions of discrimination. The Self-Rated Heath (SRH) questionnaire is a 32-item measure of current health and health behavior. The Employment Status measure is used to assess the effect of the COVID-19 pandemic on participant employment status.
The COVID-19 Psychological Impact Survey is a 3-item self-report measure of the psychological impacts of COVID-19 and associated risk factors. The Daily Activities measure contains three statements asking participants to rate the extent to which they feel impaired in their daily activities. The COIVD-19 Substance Use measure contains 4 items that ask about changes in substance use (i.e. alcohol, marijuana, e-cigarettes, and cigarettes) from before the pandemic, to now.
The Alcohol Use Disorder Identification Test-Concise (AUDIT-C) is a 3-item brief alcohol screening instrument that reliably identifies persons who are hazardous drinkers or have active alcohol use disorders (including alcohol abuse or dependence).
The Abbreviated Multidimensional Acculturation Scale is a 12-item measure that assesses an individual's level of acculturation to a host culture.
The Life Events Checklist for the DSM-V (LEC-5) and the Primary Care PTSD Screen (PC-PTSD) will be used to screen for potentially traumatic events in a participant's lifetime.

The Distress Tolerance Scale – Short Form is a 3-item measure used to measure a respondent's ability to tolerate feelings of distress. Change in Fast Food Consumption during COVID-19 will be assessed using a single item measure.
Items assessing Marijuana/Cannabis Use Behavior were selected from a statewide study on medical and recreational cannabis use (Public Health Impact of and Attitudes About Medical Marijuana Legalization in Oklahoma).
The Three-item Loneliness Scale is a 3 item scale for large-scale social surveys regarding how individuals feel about different aspects of their life.
The OASIS[122] and ODSIS[123] also will be administered at baseline.
The Mindful Attention and Awareness Scale (MAAS) is a 15-item measure used to measure conscious mindfulness.

Follow-up assessments:
Following completion of the baseline assessment, the app will automatically begin prompting twice daily EMAs for 6-months. Participants will complete two scheduled daily ecological momentary assessments (EMAs) during the intervention and continued assessment periods that will guide a just-in-time approach to immediate, personalized behavioral health care (please see EMA types section below). *Assessments will be completed remotely and no in-person study visits will be required.*

Moreover, Participants will complete follow-up assessments at 3- and 6-month post-baseline (i.e., end-of-treatment and end of 3-month continued monitoring period) using the Insight™ app. These assessments will include a qualitative interview for selected participants. The follow-up surveys will be distinguishable from EMAs (i.e., a new "Follow-up" button will appear on the app home screen (both groups) 3- and 6-month post-baseline and participants will click this button to initiate the assessment). Participants will receive a daily alert from the app to click the "Follow-up" button until the assessment is completed. Like the baseline, the follow-up assessments will include the PSS-4, PHQ-4, HRQOL, F-SozU K-6, MSSS, Covid-19 Vaccine Hesitancy Survey, Additional Aim 1 Measures, FSQ, BRFSS, Frequency of Attendance at Religious Services, Discrimination Burden, SRH, Employment Status, COVID-19 Psychological Impact Survey, Daily Activities, Change in Fast Food Consumption, Three-item Loneliness Scale, COVID-19 Substance Use, AUDIT-C, Marijuana/Cannabis Use Behavior, EDS, CRBS, SDS, , PEG Scale, , , , SSASI, OASIS, ODSIS, and Fear of COVID-19 (see above for description of measures). Additionally, the 10-item System Usability Scale[156] will be incorporated to assess perceptions of the usability of the apps (i.e., intervention and control). Lastly, the 6-month follow-up assessment only will include two demographic questions taken from the Demographic/Background Information Questionnaire.

If a participant does not respond to the app prompts to complete the follow-up assessment, he/she will be contacted via call, text, and email to remind them. Selected participants will complete a qualitative interview (i.e., phone call or Zoom) to collect qualitative data on the utility of EASE and the control app and methods for improvement for a next generation (Note: the date and time of this call will be scheduled at baseline and will appear at the top of the app home screen). We will use an interview structure and open-ended response style, like our previous studies. Further, we will use a modified quota sampling strategy. Specifically, 20-30 participants from each racial/ethnic group within the intervention and control conditions across a sampling time frame will be interviewed. This sampling strategy distributes interviews evenly across the project to minimize selection bias within each category. If participation is less than 100%, the sampling strategy will be accommodate depending on

response rate. We anticipate a high response rate based on our previous projects. This protocol has been successful in our previous research (e.g., 83% app-based follow-up completion and remote qualitative interviews in a 6-month smartphone-based intervention). Sample size is estimated based on the depth of data collection with individual participants, the diversity of participants, and project objectives. Qualitative experts advise estimating 20-30 participants per group which can be revised based on data quality. In this sequential explanatory mixed methods study, the qualitative data will complement the in-depth longitudinal quantitative data which is the primary focus of the project. The objectives for the qualitative data will be to make recommendations for future mHealth research, and compare experiences of participants from different race/ethnic backgrounds. The brief qualitative interviews will be recorded and transcribed following completion and read to monitor data quality. If the early interviews result in more complex data than anticipated, the sample size and density of the sampling strategy will be revised (e.g., oversampling racial/ethnic minority groups that reveal unique app experiences). The qualitative interviews will be recorded and securely stored for qualitative analysis (or completed by the participant via REDCap survey if a medical condition prevents them from being able to speak for long periods of time). Recordings will be transcribed by internal staff, Microsoft Transcribe, or by approved contractors. When using Microsoft Transcribe, all transcriptions will be reviewed by study staff. All participants, regardless of treatment condition, will be compensated for completing the baseline assessment ($20), 3- and 6-month follow-up assessments and qualitative interviews if selected ($50 each), for referring new participants ($10 per eligible and randomized participant up to $50), and daily EMAs (on a weighed schedule described below).

At the conclusion of the study, participants who were loaned smartphones will be provided a pre-paid padded envelope to return the phone and charger. There will be no consequences to participants who do not return their study phone to the research team at the end of the study. Participants that lose study phones will be offered a second study phone. At the conclusion of the study, resources will be provided to those who are interested in getting a smartphone for reduced rates- we will connect participants with the Lifeline program, which offers discounted telecommunications service to low-income individuals. (for more information, please visit https://www.fcc.gov/general/lifeline-program-low-income-consumers)

Assessment Schedule:

Table 3. MEASURES for Phase 1

MEASURE	ITEMS	FULL BATTERY ASSESSMENTS			EMA ASSESSMENTS
		Screen	Base	3- and 6- Month FU	MEASURE
EASE Measures					
Descriptive Variables and Moderators					**Morning Daily Diary**
Demographics-Treatment History Questionnaire (DTHQ; descriptive)	24	24			Sleep (4)
					Alcohol Consumption
Additional Phone Screener Items	4	4			Cigarette Consumption
6CIT (eligibility)	7	7			Marijuana Use
Rapid Estimate of Adult Literacy in Medicine-Short Form[138] (eligibility)	9	9			Fast food consumption
Demographic/Background Information Questionnaire	21		21	2 (6- Month FU Only)	Other Substance Use SSASI (2)
Sheehan Disability Scale (SDS)[16] (A.1: H1)	4		4	4	Prescription Medication Consumption
System Usability Scale (A.3)	10			10	Discrimination Experience (3)
4-item Perceived Stress Scale	4		4	4	Affect (15)
Everyday Discrimination Scale (EDS)[139] (A.2: H3)	6		6	6	Pain Level

Coronavirus Racial Bias Scale (CRBS)[140] (A.2: H3)	4		4	4	Ability to Cope with Stress
The Patient Health Questionaire-4 (PHQ-4)	4		4	4	Social Support
Health Related Quality of Life (HRQOL)	3		3	3	Location
The Perceived Social Support Questionnaire (F-SozU K-6) (A.2: H3)	6		6	6	**Evening Daily Diary**
MacArthur Scale of Subjective Social Status (A.2: H.4)	2		2	2	Physical Activity (2)
COVID 19 Vaccine Hesitancy Survey	15		15	15	News
Additional Aim 1 Measures	4		4	4	Money
Financial strain questionnaire	9		9	9	Hours Away from Home
Behavioral Risk Factor Surveillance System (BRFSS) Inadequate Sleep Questionnaire	5		5	5	Course of your day (2)
Frequency of Attendance at Religious Services	2		2	2	Amount eaten
PEG Scale[143] (A.3)	3		3	3	Argument
Affect Constructs					Affect (15)
Overall Anxiety Severity and Impairment Scale (OASIS)[122] (A.1: H1)	5	5	5	5	Pain Level
Overall Depression Severity and Impairment Scale (ODSIS)[123] (A.1: H1)	5	5	5	5	Ability to Cope with Stress
SSASI[171] (A.2: H3)	5		5	5	Location
Discrimination Burden (A.2: H.4)	4		4	4	**Sunday Morning Diary**
Self-Rated Health Questionnaire	33		33	21	Self-rated health questionnaire
Employment Status (A.3.b)	3		3	3	Optimism towards the future
Fear of COVID-19[145] (A.2: H3)	5		5	5	App Quality (3)
COVID-19 Psychological Impact Survey	3		3	3	OASIS (5)
Daily Activities (A.1: H.1)	3		3	3	SSASI (5)
Change in Fast Food Consumption during COVID-19	1		1	1	PSI (8)
COVID-19 Substance Use (A.3.b)	4		4	4	ODSIS (5)
AUDIT-C	3		3	3	**Report Distress**
Marijuana/Cannabis Use Behavior	6		6	6	Affect (15)
Abbreviated Multidimensional Acculturation Scale (A.2)	15		15	15	Location
LEC5 & PCPTSD-5	6		6	6	Pain Level Ability to Cope with Stress
Three-item Loneliness Scale	3		3	3	
Mindful Attention Awareness Scale (MAAS)	15		15	15	**Report COVID-19 Symptoms**
Total items	273	54	209	188	Current Symptoms Exposure to someone with COVID Loss of taste/sense of smell
Note. Screen = REDCap or Phone Screener; Base = Baseline; 3- and 6-Month FU = 3- and 6-Month Post-Baseline Follow-up. *Indicates items that are only collected during the morning EMA. **Indicates items that are only collected during the evening EMA. Please see EMA types below for more information.					

EASE App Features and Treatment Components. See Table 2 for app components. EASE offers

Table 2. Comparison of EASE and Control conditions

App Components	EASE	Control
EMA	X	X (add on for this study)
COVID-19 monitoring and intervention	X	X (add on for this study)
AS psychoeducation	X	
On demand tips and exercises		
Coping with mood	X	X
Coping with stress	X	X
Interoceptive exposure	X	
Guided relaxation	X	X
Inspirational messages	X	
Challenge Automatic	X	

Thoughts		
Tailored treatment messages in real-time	X	

clinical grade care by integrating standard CBT with a transdiagnostic treatment for AS reduction. Individuals randomized to the EASE group will receive: 1) scheduled treatment, 2) scheduled and cued interoceptive exposure sessions, 3) on-demand intervention content (i.e., how to cope with symptoms of anxiety and depression; cognitive restructuring exercises; guided relaxation videos), and 4) tailored treatment messages based on responses to EMA items. Information about frequency of resource use and length of time spent viewing EASE intervention content will be collected through Insight™.

Scheduled Treatment. During the baseline call, participants will indicate the best times for 18 3-7 minute treatment videos that focus on AS reduction (adapted from traditional AS reduction treatments)[89] and relaxation training videos to manage negative affective states (from our previous studies). Two videos will be delivered through the EASE app during each of the first 9-10-weeks of the intervention (e.g., 6:00 pm on Monday and Wednesday). Sessions will be cued at the participant selected scheduled time and 3 additional times (i.e., every 15 minutes) if the cue is not acknowledged. Participants will have the option to delay/reschedule videos or watch them before the scheduled day/time (see EASE home screen in Figure 2). Videos can be re-watched if desired (Insight will record the date/time when each video is watched, both initiation and completion). Eight of the 18 brief (3-7 minute) videos provide psychoeducation on: the role of AS in interoceptive stress; the CBT model of anxiety/depression and interoceptive stress; procedures for each intervention module; coping mechanisms to avoid experiencing negative emotions (e.g., chronic stress due to sociocultural stressors); fear-avoidance hierarchy for specific stressors (e.g., bodily stress or stress burden due to experiences of racism or discrimination); and interoceptive exposure techniques. Six videos focus on the relation between COVID-19 and anxiety/depression and the role of AS in these relations as well as utilizing AS-reduction strategies to mitigate the impact of COVID-19 related stress on mental health. Each video also presents known disparities regarding COVID-19 and the potential impact on mental health disparities. Four videos focus on relaxation training to help mitigate the impact of stress related to discrimination, general life events, and COVID-19-specific stressors on heightened symptoms of anxiety and depression. The final 2 weeks of treatment conclude with provided response-prevention prompts to remind participants to use and practice skills learned, as well as redirecting and reminding them to review specific intervention content.

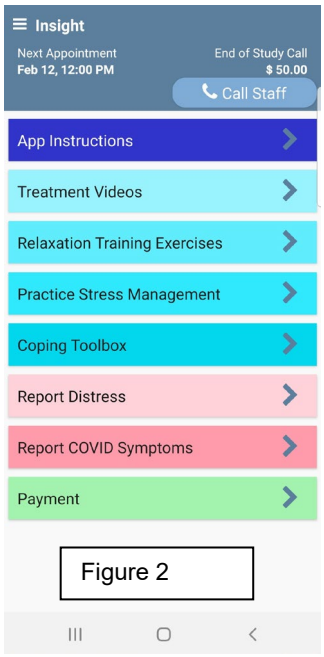

Figure 2

Exposure sessions. Internet- and smartphone-based interoceptive exposure are well tolerated, acceptable, and effective.[107,131,132] We will target AS through graduated exposure to anxiety and distress-provoking situations and response prevention. These exposure exercises were originally created for a previous app-based treatment developed by our team for AS-reduction (e.g., over-breathing, straw breathing, running in place, chair spinning, and head rush). The EASE app will cue the participant to begin the exposure session at the designated time and then the app will guide participants through exposure exercises. Participants will learn to manage negative affect and stress during elevated distress states without acting on acute motivation to supress distress. In the exercises, the app guides the participant through interoceptive exposures by explaining the activity, normalizing the physical symptoms experienced during the exercise, and relating this experience to the increasing tolerance of physical symptoms (e.g., anxiety, depression), as well as helping to cope with experiences of discrimination. When the participant is ready to begin, the app will assess level of distress (0-100 scale), begin a countdown for a specified amount of time for the

exposure, and re-assesses level of distress (0-100 scale) once the countdown has expired. This is immediately repeated to ensure habituation to feared sensations. Participants will complete brief questions about the length, engagement, and usefulness of the exposure, and they will be encouraged to continue practicing these exposures daily (i.e., "Practice Stress Management" option on the app home screen). Exposures will incorporate graduated elements to safely elicit strained breathing, racing heart, dizziness, and mild disorientation. These exposures were selected to elicit symptoms that may increase worry about potential COVID-19 infection, particularly among racial/ethnic minority populations.
EMAs with tailored real-time treatment messages. During the 3-month intervention period, a message will be delivered at the end of each EMA (2 per day). When participants provide a pattern of responses that are suggestive of heightened emotional distress (e.g., answering, "neutral, agree, or strongly agree" when asked to rate how much they agree with the statement, "Right now, I feel depressed" using a 5-point Likert scale.), they will be prompted to complete an on-demand exercise (e.g., cognitive restructuring, guided relaxation video). The type of message that is delivered (e.g., coping with depression, coping with anxiety, coping with COVID-19 related anxiety) will be recorded in the database, so we may determine if the message attenuated the targeted symptom (assessed during the next EMA). Maladaptive automatic thoughts will be assessed in EMAs. EMAs will capture participants' beliefs about internal and/or physical sensations experienced. When participants endorse maladaptive cognitive processes, EASE will use response skip patterns to encourage challenging of maladaptive thoughts and to develop more balanced responses. Interactive exercises to guide the participant through the process of challenging dysfunctional thoughts are to be also available 'on demand.' Additionally, participants will be instructed to review and practice interoceptive exposure exercises to further normalize symptoms of anxiety and depression as well as consider the uniqueness of these symptoms relative to COVID-19 symptoms.
On demand features. We have created a menu of on demand intervention content that is available through clicking buttons on the EASE home screen. Specifically, participants can use the Coping toolkit button to access: 1) tips on coping with stress and anxiety, 2) relaxation exercises, 3) help with challenging unhelpful thoughts, 4) coping with COVID-19, 5) coping with loss and grief, 6) coping with discrimination, 7) coping with sadness and depression, and 8) distraction exercises. Participants are instructed to click the Treatment Videos button to access educational content on how to cope with stress, anxiety, and depression. In addition, they will be instructed to click the Stress Management training button to complete exercises that are designed to help overcome the negative feelings of stress. Further, participants will receive a coping focused message at the completion of the participant-initiated "Report Distress" EMAs. Finally, participants are instructed to click a "Report COVID-19 Symptoms" button to report any COVID-19 symptoms they are experiencing to research staff at any time throughout the study.

Instructions on how to use app functions will be available to participants in the home screen (i.e., App Instructions) which will be accessible at all times. Moreover, participants will also be able to contact the research staff when needed using the "Call Staff" function of the insight app if they have any questions. The Insight platform respects users display settings and participants will also be able to make font sizes bigger if needed.

Standard-of-Care Control. Participants randomized to the control condition will be prompted to download the Insight™ app and enter a unique activation code provided by the research team. Upon entering this code, participants will be granted access to the baseline assessment. Upon completion of the baseline assessment, the app will ask for a code. Participants will receive the code for the control

app from the research team. The control app was built using the Insight platform. Participants assigned to the control app will have access to: 1) a series of educational videos that discuss meditation techniques, mindfulness exercises, and stress reduction exercises, 2) a feature that allows participants to report when they are experiencing heightened stress, anxiety or depression, and 3) a "Report COVID-19 Symptoms" button that allows participants to report any COVID-19 symptoms they are experiencing to research staff at any time throughout the study. If a symptom cluster consistent with COVID-19 is detected, an encrypted email will be sent to the research team and they will work with the participant to help them find a local testing center. Instructions on how to use the app will be available to participants on the home screen, and will accessible at all times. Additionally, participants will be able to call study staff by pressing the "Call Staff" button on the study home screen. Participants will receive 2 daily EMAs during which they will be prompted to watch aforementioned educational videos twice per week. Following the intervention period, participants will be encouraged to continue to practice the meditation, mindfulness, and stress reduction techniques they have learned, report moments of heightened stress, depression, or anxiety, and report any COVID-19 symptoms they experience.

Ecological Momentary Assessments (EMA). EMAs are currently the most accurate way to measure phenomena in real-time, natural settings.[158,159] EMA items will identify fluctuations in key variables that predict study outcomes with less bias than traditional in-person assessments. EMA data will be used to identify moments of distress (e.g., anxiety/depression), tailor EASE treatment, and identify treatment mechanisms.

App Configuration. The mHealth Shared Resource (Businelle is the founding director) at the OUHSC and NCI Designated Stephenson Cancer Center (SCC) has developed the Insight™ mHealth Platform which enables researchers to **RAPIDLY** create studies (e.g., most studies are created within 1-2 weeks) that can use EMA and sensor data (i.e., activity monitor) to identify environmental, cognitive, affective, physiological, and behavioral antecedents of health risk behaviors (e.g., smoking, heavy alcohol use, inactivity / obesity) and deliver context-specific adaptive interventions in real-time (see more about Insight™ here: [160]). The mHealth resource currently employs 11 individuals, including 7 senior programmers (computer scientists/engineers) who develop and maintain our cross-platform Insight™ app and relational databases. To date, the mHealth resource has supported 65 studies including 35 with funding from the NIH. Across studies, thousands of participants have used the Insight™ app. EASE Intervention adherence will be objectively assessed by examining components used by each participant (e.g., videos watched, completed exposure exercises). To access perceived engagement with EASE and control intervention, participants will answer questions about app features used and time, in total, spent using the app each week during the Sunday morning EMA assessment. Similar methods have been used to assess app engagement in past work.[133]

EMA Types: The EMA methodology for this study will be similar to what we have used in our previous studies, and by other researchers.[109,110,114,121,161-170] Each EMA will ask about current emotional, physical, and behavioral symptoms, as well as COVID-19 symptoms, and will take approximately two minutes to complete. Two types of EMAs will be used: time-based sampling (i.e., daily diary) and event sampling. Time-based EMAs will be prompted and initiated by the phone two times per day during the 6-month study period (we have had great success with this type of EMA schedule in previous trials, e.g., ~70% EMA compliance over 6 months; see Table 3 for EMA constructs). Also, participants will be instructed to self-initiate event sampling EMAs to record Distress and new COVID-19 symptoms. All EMAs will be date and time stamped for future analyses.

Time-Based Sampling EMAs: Daily diary EMAs will be prompted by the smartphone twice per

day (i.e., morning daily diary 30 minutes after the participant's pre-set wake time; end of day daily diary 75 minutes before the participant's pre-set bedtime). The phone will ring and vibrate to cue these EMAs for 5 minutes (i.e., alternating between 30 second alerting and silence periods). If the participant does not respond to the daily diary prompts, the EMA will be automatically rescheduled (up to 2 additional times) 15 minutes later. Questions ask about current symptoms of anxiety and depression, medication use, current thoughts/affect/behaviors, social support, discrimination experiences, sleep quality/quantity, fear of COVID-19, daily activities, fast food consumption, and current COVID-19 symptoms. Participants will rate their emotional state by indicating the extent to which they agree or disagree with each of 15 statements (using a 5-point scale from strongly disagree to strongly agree): I feel stressed, happy, angry, tired, afraid, relaxed, sad, bored, worried, lonely, calm, depressed, overwhelmed, energetic, and anxious (from the circumplex model of affect).[171] Participants also will indicate current environment/social setting. During the weekly Sunday Morning EMAs participants will answer questions about their health behaviors, optimism towards the future, quality of the app, their levels of anxiety and depression, and COVID-19 related items (see Table 3).

Event Sampling EMAs: All participants will be asked to initiate "Report Distress" EMAs and answer Core EMA items when they perceive a heightened level of depression and/or anxiety (see Table 3). Participants will be instructed to answer questions based upon immediate thoughts/feelings. EASE participants will receive unique intervention content when they report elevated depression and/or anxiety symptoms. Intervention/coping messages and video content will be different each time the "Report Distress" button is clicked (this component is consistent with 8 of our previous trials on various topics including relapse prevention [e.g., Smart-T, Smart-T Alcohol, Phoenix, MASP, M-ICART] and mood management interventions [e.g., Persist]). Additionally, all participants will be asked to initiate a survey (by clicking the "Report COVID-19 Symptoms" button in the app) if any new COVID-19 symptoms arise between the morning and evening daily diaries. **NOTE:** Our previously developed COVID-19 risk detection algorithm will advise participants to get a test for COVID-19 when elevated risk is detected. The app will immediately trigger an automated and encrypted email to study staff to call the participant and assist with obtaining a COVID-19 test (if desired by the participant).

The EASE app content was created by Dr. Businelle and Dr. Zvolensky. Moreover, all EASE app content in this study will be accessed through the Insight platform, which is owned by the Oklahoma University Health Sciences Center (OUHSC). The EASE app will only be available to research participants.

The control app used in the control condition was created by Dr. Businelle and Dr. Zvolensky. All content found in the control app for this study will be accessed through the Insight platform, which is owned by the Oklahoma University Health Sciences Center (OUHSC). The control app will only be available to research participants.

11.0 Setting

Participants will be screened for eligibility via phone and data will be entered into REDCap. All screening data will be will be collected online via REDCap. The study investigators will be the only ones who have access to the data collection portal. Qualitative interviews will be recorded and transcribed for analysis.

12.0 Risks to Subjects

Participation in this study poses minimal risk to participants. However, one potential, although unlikely, risk to participants is loss of confidentiality. The severity of harm in the case of loss of confidentially may range from mild to severe depending upon the individual and the specific circumstances. However, the risks of participation in the study are similar to participation in usual in person mental health clinic care, as loss of confidentially may be experienced in either case. Other possible adverse events might include compromised data security and discomfort related to being asked study questions. The research team will monitor this risk and the others listed below and report adverse events immediately to the IRB.

Each participant will be assigned an identification number that will be utilized in place of names in all electronic data files. The sheet or datafile containing the links between participant names and identifiers will be kept in locked filing cabinet and/or password protected digital files on encrypted university computers and will be destroyed 12 months after data collection has been completed. All electronic data (with names omitted) will be maintained on the investigator's computers, and all computers and electronic files will be encrypted and password protected. Identifiable participant information will not be released to any party outside the research team at any time.

In the unlikely event that a participant experiences severe symptoms while participating in the study, a protocol has been developed to address this concern. If a participant experiences severe symptoms, mental health referral information for providers within a 50-mile radius of their home location will be provided to participants. The potential for discomfort associated with being asked personal questions regarding thoughts and behaviors will be minimized in the following ways:

i. By informing participants of the nature of questions to be asked, participants will not be caught unaware by the topics covered and can decline participation if such topic areas are known to be personally uncomfortable.
ii. Only measures that have been validated or used in prior studies will be used. None of the proposed instruments have been known to evoke serious emotional reactivity.
iii. Participants will be consistently reminded that they are free to skip any baseline/follow-up questions they do not wish to answer, without penalty.
iv. All participants will be reminded during consent they may contact study staff with any questions or concerns that arise during the survey.

Lastly, the time commitment to participate in the study may be burdensome to participants. However, participants will be informed that they can leave the research at any time it will not be held against them.

13.0 Potential Benefits to Subjects

First, the overall cost/benefit ratio is highly favorable for participants. All participants will have the opportunity to examine and improve their ability to effectively manage their mood and stress through the intervention program. Second, the costs of completing the study have been minimized through our use of procedures for maintaining confidentiality, and minimizing the risk of adverse study reactions. Third, the societal benefits of the proposed research are better

understanding how to develop a mobile mental health intervention that is personalized and focused on improving anxiety and depression. Fourth, the implementation of smartphone-based interventions to address anxiety and depression could have a positive impact on public health policy for minorities (e.g., American Indians, Hispanic, African Americans). Further, it is possible that EMAs will identify key factors that predict mental health symptom exacerbation, and this information may be used to improve future COVID-19-specific mental health interventions for White, African Americans, Hispanic, and American Indians. Finally, all participants, regardless of group assignment, will complete a daily COVID-19 screener. This information will have access to a COVID-19 symptom screener and when our previously developed algorithm indicates heightened risk, participants will be notified and assisted (if desired) with scheduling a COVID-19 test.

14.0 Withdrawal of Subjects

There are no anticipated circumstances under which subjects will be withdrawn from the research without their consent.

15.0 Costs/Payments to Subjects

In addition to compensating participants for completing the Baseline (i.e., $20), and 3- and 6-month post-baseline assessments, which will include a qualitative interview over the phone for selected participants (i.e., $50 each), participants will be compensated for completing daily EMAs for 6-months. Specifically, those who complete 50%-74% of prompted EMAs each month (2 per day x 30 days = 60 monthly EMAs) will receive $20, those who complete 75%-89% of assessments will receive $30, and those who complete 90% or more of their EMAs will receive a total of $40 for that month. Additionally, participants will have the ability to earn up to $50 for referring people to our study. Participants will have the ability to earn $10 for each person they refer who is deemed eligible and randomized into the study, up to $50. Participants will be compensated through a reloadable Greenphire MasterCard. These cards can be used anywhere MasterCard is accepted and participants may use these cards to withdraw their compensation from a bank. This convenient and auditable method of payment is preferred by participants and study staff. Cards will be purchased by the study team and mailed to participants following their baseline assessment and reloaded monthly based upon compensation earned.

16.0 Confidentiality

Consent forms with identifying information will be completed via RedCap, encrypted, and stored on university computers. A password protected computer file will contain information linking participant names to their assigned numbers. Only the researchers will have access to this information.

17.0 Provisions to Protect the Privacy Interests of Subjects

Participants will be consistently reminded that they are free to skip any baseline/follow-up questions they do not wish to answer, without penalty. Participants will not need to answer any questions that they find intrusive to their privacy.

Participants will answer questions in a location and time of their choosing. Upon receipt, study phones that are returned by participants will be factory reset. Phones will not be mined or reviewed for non-study related data.

18.0 Informed Consent Process

The informed consent process will be completed via phone. During this call, study staff will verify that each individual meets the study inclusion criteria, staff will review study details with each individual; and interested individuals will complete the informed consent process (signatures will be collected digitally via REDCap).

The information to be provided to the participants over the phone will be that which is included in the uploaded consent document (please refer to consent form uploaded to the Local Site Documents). The consent document will be displayed to participants over REDCap and participants will be able to read and review all information while on the phone with a research assistant who will ensure the participant understands the research and has no questions. Thus, all participants will be provided with written information describing the research to be provided to the subject

The research will present no more than a Minimal Risk of harm to subjects and will not involve procedures for which written consent is normally required outside of the research context.

Participants will be informed that qualitative data collected through the qualitative interview will be transcribed through transcription company Civicom. Accordingly, Civicom will readily review and accept clients and partners ensuring that PHI shared with them will not be compromised, as they are committed to confidentiality and the protection of health information for individuals, clients, customers and partners. Moreover, we will ensure participants are aware the only data being shared with Civicom is the audio recording of qualitative interviews, and as such, no personal information will be shared with Civicom unless this information is mentioned during the interview process.

19.0 Process to Document Consent in Writing

The consent form will be reviewed with the participant by a member of the study staff via phone. Participants who choose to take part in the research study will sign consent forms electronically via REDCap.

REDCap is a secure, web-based platform which allows for safe, secure and easy sharing of collected data within and across institutions for multicenter trials as it requires user authentication and can assign data access rights based on user role, allows for field-level data validation, and has mechanisms for ensuring data quality and integrity. It offers a digital method to acquire and store participant consent by implementing the study's consent form through an online survey that will display a PDF copy of the consent document (please refer to uploaded consent form in local site documents) that can be accessed by the participant through a computer, mobile phone, or tablet. Participants will be able to read and review the consent form virtually and will do so while on the phone with a research assistant who will ensure the participant understands the study procedures and who will answer any questions the participant may have.

Participants who would like to participate will be able to 'sign' their consent form electronically by typing in their name or by utilizing REDCap's 'Signature' field type on the survey. Signed documents will be protectively stored to our server and participants will **not** need to email any signed documents to the research team. Participants will be mailed a signed copy of the consent form.

20.0 Data Management

Data Management Organizational Structure. Confidentiality is assured by several factors. Most importantly, participants will be identified on only by participant identification number (names and ID numbers will be stored in encrypted and password protected data files on the investigators firewalled computers). Additional measures to ensure the confidentially of study data include the following: access to databases (REDCap and InsightTM) will require complex passwords. When data are accessed, the user id, password, date, and time are logged. Each user of the systems will be assigned unique user-IDs.

Our study procedures prevent potential fraudulent surveys, as they consist of speaking with participants on the phone before they are enrolled, and all participants will need an activation code from the research team in order to participate in the study. Additionally, participants will need to provide a valid address, social security number, and date of birth in order to receive Greenphire cards.

The Insight app encrypts all data as it is collected and this data is synced to our secure servers up to four times per day. Thus, the research team can still access data collected through Insight even when a phone is not returned and may be retrieved if a phone is lost. Participant data will be collected through Insight, REDCap, and qualitative interviews will be recorded and transcribed. Recordings of transcribed interviews will be deleted within 12 months of transcription. All data will be stored in password protected and encrypted computers. The Insight app is encrypted within the smartphone.

A copy of the collected data will be stored for at least 3 years following completion of the research study. Study data will be stored to university owned encrypted computers. Consistent with NIH requirements, we will provide de-identified data from this project to interested individuals one year following achievement of the aims of the project (i.e., publication of the main outcome papers). These data will be provided in digital format (i.e., disk) with clear labels for all variables. Requested data will be released directly by the investigators providing evidence of their institutional IRB approval for planned analyses of the data. Our team will be available to address queries. The Insight app works through an encrypted shared content management system which allows researchers from both sites to download data directly to university owned encrypted computers. Both sites are able to download study data directly. Study data collected through Insight will be saved to our laboratory drive which is set up by the UH Psychology Department's IT team. Study data will be password protected.

For recruitment through BuildClinical, they will be collecting their own data when advertising our study to participants and sharing data with the University of Houston and University of Oklahoma study teams. Data collection will be through our pre-screener link. Collected data will

include: (1) Full name, (2) Phone number, (3) Phone number (secondary), (4) Email address, (5) Age, (6) Date of birth, (7) Ethnicity, (8) Race, and (9) Gender assigned at birth. BuildClinical does not interact with data outside of sending the data to the University of Houston and the University of Oklahoma. BuildClinical's Secure Socket Layer (SSL) software encrypts all inputted information and keeps the information private. All of BuildClinical's systems are HIPPA-compliant and have been approved by the Office of Veterans Affairs and the National Institutes of Health. Study teams will not be sharing data with BuildClinical that will need to be protected by the 3rd party. Upon request, BuildClinical can remove data from their platform.

Qualitative data collected through the qualitative interview will be transcribed through transcription company Civicom. Civicom acts as a Business Associate of Covered Entities as defined under HIPAA. Accordingly, Civicom will readily review and accept clients and partners ensuring that PHI shared with them will not be compromised. Moreover, Civicom is committed to confidentiality and the protection of health information for individuals, clients, customers and partners. Their data policies ensure that privacy and security of any health information is protected in all forms, with particular care in controlling the confidentiality, storage and access to electronic Protected Health Information. They have achieved this by implementing security standards, administrative, technical, and physical safeguards, organizational requirements, and requirements for documentation, policies and procedures. Civicom standards are maintained and improved by continuous review and audit of internal processes and business agreements, with the aid of external consultants and specialized staff dedicated to data privacy. Additionally, Civicom provides training to all members of its workforce on policies and procedures with respect to PHI, as necessary and appropriate for them to carry out their job responsibilities. Moreover, it must be noted that the only data being shared with Civicom is the audio recording of qualitative interviews, and as such, no personal information or PHI will be shared with Civicom unless this information is mentioned during the interview process of any participants.

Data analysis overview: Hypotheses for Aims 1 and 2 will be examined using latent growth models (LGM),172 multilevel structural equation models173 (MSEM) and latent difference score174 models using MPlus 8.0.175 To simplify subsequent sections, an overview of the common data analysis elements is presented first. Data will first be examined for multivariate normality and outliers to determine the most appropriate estimator. The maximum likelihood (ML) estimator will be used if data are approximately normal. Robust maximum likelihood (MLR) will be used if the data are not multivariate normal. We anticipate some participant attrition during the trial. Missing data will be handled in all analyses using direct ML techniques within MPlus under a missing at random (MAR) assumption.176 Modern missing data techniques such as direct ML increase statistical power and provide more accurate estimates of model parameters and standard errors and are the recommended intent-to-treat approach for clinical trials. LGM will generally be used to model outcomes collected at major assessments. MSEM will be used to further examine the longitudinal course of outcomes and hypothesized mechanisms of action as MSEM is ideally suited for disentangling within and between individual variance in order to more precisely estimate main effects, lagged effects, and indirect effects in intensive longitudinal designs. Evaluation of model fit in the LGM/MSEM models will be examined using fit diagnostics (i.e., standardized residuals) and common fit statistics (i.e., root mean square error of approximation) following the associated cutoff criteria recommended by Hu & Bentler.177 We will assess the equivalence of the treatment groups on key baseline

variables (demographics and psychological variables); variables on which the groups differ will be used as covariates in the final analyses. We will also examine attrition from the study as a dichotomous outcome and use logistic regression to determine if treatment assignment predicts attrition.

21.0 Sharing of Results with Subjects

Study results will not be shared with participants.

22.0 Resources

Dr. Zvolensky has published over 750 peer-reviewed articles and books/book chapters on the co-occurrence of anxiety and stress-related psychopathology with substance use disorders, health behavior problems, and physical illness. He has utilized a variety of methodological tactics in his research program, including community-based participatory research (CBPR), laboratory studies, epidemiologic-field (cross-national and prospective), Ecological Momentary Assessment (EMA), and randomized clinical trials. He has developed culturally tailored interventions in past projects for racial and ethnic minority groups. A large percentage of his recent work has focused specifically on smoking among African American and Latino populations. He has been involved in over 60 NIH grants as PI, Co-PI, or co-investigator, and therefore, has extensive experience leading large and multi-team projects.

Dr. Garey's research employs advanced methodological designs to elucidate risk and protective factors of addictive behavior and treatment outcomes. Dr. Garey has published over 115 peer-reviewed articles and books/book chapters on topics within her area of research and served as PI on several federally and privately funded grants, including a stage I trial of a technology-based intervention for mood and substance use. Many aspects of her research program focus on health behavior change models, including elucidating biopsychosocial determinants of substance use and mental health. She has collaborated with Drs. Zvolensky, Businelle, Vujanovic, and Gallagher. Dr. Garey assisted extensively with the refinement of the current research idea and proposal and will serve as the project coordinator.

Dr. Gallagher has published over 110 peer-reviewed articles and book chapters primarily focusing on transdiagnostic treatments, mechanisms of change, and resilience factors for emotional disorders. Dr. Gallagher's training and expertise is in both clinical and quantitative psychology, and he has extensive experience with the proposed methods of data analysis, particularly the examination of outcomes and mechanisms of change in clinical trials and EMA studies, including work expressly focused on tobacco. He has served as both co-investigator and biostatistician on NIH, VA, DOD, and foundation grants focusing on clinical trials for emotional disorders and experimental psychopathology work examining how factors such as anxiety sensitivity contribute to the development and maintenance of depression and anxiety disorders. He has multiple ongoing collaborations with Dr. Zvolensky that have resulted in publications and grants and has successfully collaborated with Drs. Businelle, Garey, and Vujanovic on peer-reviewed articles in collaboration with Dr. Zvolensky. He will have primary responsibility for overseeing the data analyses for this project, will oversee the randomization, and will also advise on any statistical or other methodological issues that arise during the trial.

Dr. Vujanovic has published over 160 peer-reviewed articles and book chapters primarily focusing on trauma, stress, and substance misuse among high-risk populations (e.g., first responders, human trafficking victims). Dr. Vujanovic's expertise offers a unique and complementary addition to the team, as she has long-standing clinical and scholarly experience with the socioenvironmental contexts of low SES African Americans and other underrepresented groups. Across both clinical and research contexts, she has extensive experience in the application of cognitive-behavioral approaches for the treatment of psychiatric conditions, namely traumatic stress, and substance use. Further, she has frequently recruited and retained populations who identify as racial/ethnic minorities in intensive treatment work on addictive disorders. She has multiple ongoing collaborations with Dr. Zvolensky that have resulted in publications and grants and has successfully collaborated with Drs. Gallagher and Garey on peer-reviewed articles in collaboration with Dr. Zvolensky. She will have primary responsibility for overseeing the retention of the sample and will also advise on other methodological issues that arise during the trial.

Dr. Michael Businelle is the primary investigator in charge of the TSET Health Promotion Research Center in Oklahoma. Dr. Michael Zvolensky is the primary investigator for all subsites.

23.0 Additional Approvals

N/A