Brief Enhanced Anxiety Sensitivity Treatment: A Pilot Study

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Abstract

The impact of the COVID-19 pandemic on behavioral health and associated functional impairment is well-documented. Based on data from past national/regional crises, the impact on emotional distress and functional impairment will continue unabated for many people. Yet, the increased use of telehealth and mobile apps in the Veterans Healthcare Administration (VHA) provides an unprecedented opportunity to quickly and efficiently ameliorate extreme emotional distress through brief evidence-based interventions. Anxiety sensitivity, or fear of anxiety sensations, amplifies the experience of emotional distress. People high in anxiety sensitivity fear that bodily sensations associated with anxiety are catastrophic, setting up a vicious positive feedback loop leading to increased distress and/or avoidance of anxiety-provoking situations and ultimately functional impairment. There is robust evidence that anxiety sensitivity contributes to increased emotional distress and functional impairment during the COVID-19 pandemic.

Cognitive behavioral therapy (CBT)-based interventions for anxiety sensitivity have demonstrated efficacy in reducing anxiety sensitivity. However, this efficacy has not translated to effective delivery of these interventions. Anxiety sensitivity interventions either require many in-person sessions with a trained clinician making them costly and time-intensive or are online self-help programs which results in deficits in treatment uptake and reports of patient disengagement. We have developed Brief Enhanced Anxiety Sensitivity Treatment (BEAST) as a brief one-session intervention that can be delivered effectively by a clinician via telehealth and augmented with a mobile app. BEAST includes psychoeducation, cognitive bias modification, and interoceptive exposure exercises designed to reduce sensitivity to anxiety-provoking stimuli, delivered virtually with a CBT-trained clinician.

The proposed study will be the first to provide preliminary data for BEAST among Veterans with elevated anxiety sensitivity reporting functional impairment. The study's first aim will be to adapt an existing brief intervention for anxiety sensitivity for virtual delivery within the VA and augmentation via mobile app to increase homework adherence and treatment gains. The second aim will be to assess the feasibility, acceptability, and usability of BEAST among 15 Veterans with elevated anxiety sensitivity and functional impairment. It is expected that, upon completion, an intervention will be developed that effectively reduces functional impairment due to anxiety through reducing sensitivity to anxiety. Conducting this preliminary study establishes the feasibility, acceptability, and usability of BEAST using pre-existing VHA infrastructure to deliver the intervention (i.e., telehealth, mobile app). This study directly addresses RX-22-003 in that we aim to aid in the recovery from functional impairment in Veterans with elevated anxiety. Based on results of this study, we will propose a fully-powered effectiveness randomized control trial.

List of Abbreviations

BEAST – Brief Enhanced Anxiety Sensitivity Treatment

CBT – Cognitive Behavioral Therapy

CoE – VISN 2 Center of Excellence for Suicide Prevention

CPG – Clinical Practice Guidelines

ITT – Intent-to-treat

MAR – Missing at random

PROMIS – Patient Reported Outcome Measures Information System

Contents

Study Protocol

Protocol Title:

1.0 Study Personnel

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2.0 Introduction

Veterans with anxiety are likely to suffer disproportionately and unnecessarily following the COVID-19 pandemic because of anxiety sensitivity. The death toll and economic impact of the COVID-19 pandemic are staggering. Unaddressed, a mental health crisis will follow.[1] Prior natural, manmade or biological disasters have spurred long-lasting mental health impacts; already, longitudinal data on the wellbeing of people during the COVID-19 pandemic support an emerging mental health crisis. Fear and anxiety about the COVID-19 virus itself, the economic impact, and the uncertain timeline are driving the mental health impacts of COVID-19, with 45% of Kaiser Family Foundation poll respondents reporting that the coronavirus has had a negative impact on their mental health.[2] For Veterans already experiencing heightened anxiety, the duress experienced during the pandemic will exacerbate pre-existing difficulties in everyday functioning (i.e., work/school, family, household obligations). Anxiety sensitivity is an ideal target to efficiently restore functioning in this population. Anxiety sensitivity, a highly researched risk factor represented in the DSM-5 and NIMH's RDoC matrix, is defined as the fear of catastrophic outcomes due to anxiety sensations.[3] Anxiety sensitivity is associated with a broad array of anxiety, mood, and substance use pathology as well as suicidal thoughts and behaviors.[4–8] Experimental studies have verified that anxiety sensitivity exacerbates the experience of anxiety;[9–12] Individuals high on anxiety sensitivity misinterpret and overreact to stress, anxiety symptoms, and bodily sensations. Theoretical models posit that short- and long-term stressors, such as those experienced during the pandemic exacerbate the experience of negative emotions that individuals with elevated anxiety sensitivity already experience (see Figure 1).[13,14]

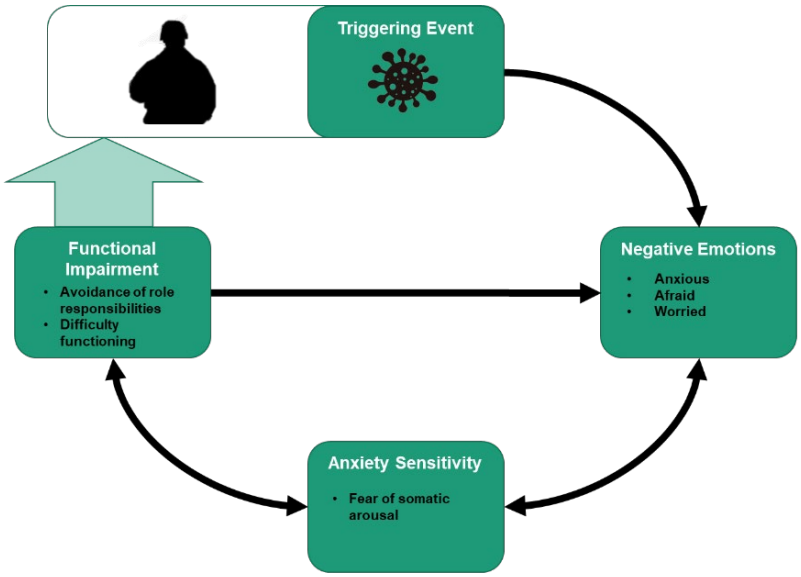

Figure 1. Theoretical model demonstrating the role of anxiety sensitivity in developing and exacerbating functional impairment.

Functional impairment during COVID-19 is common and anxiety sensitivity has been implicated as a risk factor. Anxiety sensitivity exacerbates the experience of negative emotions and increases the likelihood of maladaptive coping behaviors, including avoidance of role responsibilities, resulting in increased functional impairment. Preliminary studies we have conducted during the pandemic support this hypothesized model of anxiety sensitivity. Across three samples (Ns = 249, 368, 435), anxiety sensitivity was significantly and strongly associated with increased functional impairment related to the COVID-19 pandemic (rs = .58-.69, R2 = .34-.48) as well as increased anxiety severity (rs = .67-.68, R^2 = .45-.46). Further, Veteran status moderated these relations such that these effects were more pronounced in Veterans compared

to civilians. Manning and colleagues[15] reported that anxiety sensitivity moderates the association between anxiety and distress experienced during the COVID-19 pandemic and functional impairment in a sample of 563 adults. In a sample of 645 community adults we collected data on from May to October 2020, mean anxiety sensitivity levels exceeded clinical cutscores for moderate-to-severe anxiety sensitivity (M = 21.40, SE = 0.67), remained elevated at six-month follow-up (M = 19.61, SE = 0.75), and were significantly correlated across timepoints, R^2 = .89. Another study found anxiety sensitivity during the early stages of the pandemic predicted functional impairment one month later.[16] These studies demonstrate that regardless of the progression of the pandemic through recovery, a large minority of Veterans will retain functional impairment driven by anxiety sensitivity barring intervention.

Anxiety sensitivity can be reduced using brief CBT techniques. There is robust evidence that anxiety sensitivity is malleable using CBT techniques. Brief CBT is an ideal treatment modality to increase treatment access efficiently. Brief, computerized interventions targeting anxiety sensitivity have been shown to be efficacious and to reduce functional impairment.[17–23] However only self-help interventions are available. Pilot studies in the VA and elsewhere suggest this may not be optimal for delivery of a brief anxiety sensitivity intervention. In a study focused on dissemination of a brief computerized self-help anxiety sensitivity intervention, only 57% reported that the intervention was more than "moderately helpful" and 41% indicated they would be very likely to use the information/techniques learned during the intervention.[24] In an acceptability/feasibility trial of the same brief anxiety sensitivity self-help intervention in 22 Veterans experiencing a mild TBI and elevated anxiety sensitivity,[25] Veterans provided multiple recommendations for improvement. Relevant to the low percentage of treatment uptake when a computerized intervention was delivered, Veterans requested more opportunities to practice the skills learned during the intervention, a therapist to assist in comprehension, and inclusion of interoceptive exposure (IE) exercises. Concerns raised were consistent with the treatment literature: treatment uptake and outcomes are increased substantially when homework is completed, when a therapist is included, and when IE is practiced.[26–29] We directly address these barriers through iterative development of Brief Enhanced Anxiety Sensitivity Treatment (BEAST), a one-session intervention that can be delivered effectively by a clinician via telehealth and supplemented with a mobile app to provide opportunities to practice the skills learned in the face-to-face session.

To enhance the efficacy and ease of dissemination of BEAST, we propose two crucial improvements to our prior protocol. First, prior brief anxiety sensitivity interventions have been self-guided. BEAST is delivered via telehealth, which retains the accessibility of other brief anxiety sensitivity interventions while increasing Veteran engagement. BEAST will be delivered in a one-hour intervention by a master's level or above therapist who has experience in CBT and telehealth. Second, as practicing skills outside the session improves treatment outcomes,[30] the intervention will likely be more impactful if opportunities to practice skills learned during the telehealth session are provided. Adding **ecological momentary intervention** (EMI),[31] delivered via ecological momentary assessment (EMA), to the treatment will remind participants to apply skills they learned in the face-to-face session in a variety of real-life situations and practice IE at different times and mental states. EMI delivers the intervention remotely in real-time and in

natural settings, providing better learning through deeper processing.[32] Recent studies on depression, anxiety, and stress as outcomes indicate a medium effect size improvement through inclusion of EMI.[33–35] We expect inclusion of these elements not to impact the feasibility and acceptability of the trial compared to brief self-help interventions while translating to enhanced efficacy and ease of dissemination in our future fully-powered trials of BEAST.

3.0 Objectives

Dr. Allan was involved in the development and testing of prior computerized self-help interventions for anxiety sensitivity.[18,21,31] Since the onset of the pandemic in the summer of 2020, our group has worked with populations of anxious adults reporting distress and impairment due to the COVID-19 pandemic to create BEAST and other brief transdiagnostic treatment modules (i.e., intolerance of uncertainty, social isolation). We recently completed several focus groups in 12 adults reporting elevated anxiety sensitivity or intolerance of uncertainty. We also completed a focus group with three PhD-level therapists who use CBT as part of their daily patient regimen. Participants and therapists reported the content of the intervention was accessible, easily understood, and highly relevant to distress. Participants and therapists thought inclusion of EMA/EMI would improve participant engagement and reported they would not perceive completion of multiple surveys daily to be a burden. Participants also believed personalized content would increase engagement and assisted in developing a protocol to collect this content. Participants made several suggestions to improve delivery of the intervention, including a therapist modeling the use of the mobile app, check-ins on mobile app completion, and creating a set of questions to determine which facet of anxiety sensitivity is driving anxiety. This pilot one-arm trial will test the acceptability, feasibility, and usability of BEAST to reduce anxiety sensitivity and functional impairment in Veterans.

We are proposing the following aims:

Aim 1: Adapt an existing brief intervention for anxiety sensitivity for virtual delivery within the VA and augmentation via mobile app to increase homework adherence and treatment gains. *We will use a Delphi method to engage Veterans with elevated anxiety sensitivity and functional impairment into the design and evaluation of BEAST. We will also partner with the VA Center for Mobile Apps Research and Resources to incorporate design changes directly into the app.*

Aim 2: Assess the feasibility, acceptability, and usability of BEAST among 15 Veterans with elevated anxiety sensitivity and functional impairment. *We will assess (1) treatment satisfaction and acceptability, (2) participant recruitment and retention, (3) participant treatment adherence, (4) therapist fidelity, and (5) assessment fidelity. Further refinement will occur based on feedback.*

4.0 Resources and Personnel

Drs. Allan and Stecker will train the research team to administer verbal consent and administer and score the assessment measures through instruction and observed role play. Interventionists with at least a master's degree and prior CBT training will deliver BEAST. Drs. Stecker and Allan will train the interventionists using the PowerPoint slide deck. We will monitor treatment fidelity (i.e., adherence and competence) by audio-recording intervention sessions

(via Teams or Webex) and reviewing them in weekly supervision meetings. Weekly meetings will be provided by Drs. Allan and Stecker. The meetings will focus on all of the issues involved in study tasks including: a) recruiting participants, b) conducting interviews, c) coding interview data, d) communicating between research staff and interventionists, e) contacting participants for follow-up assessment; f) completing documentation, and g) storing and safeguarding data. To maintain blinding, separate meetings among interventionists and the coordinator will be done as needed. The interventionist will complete intervention sheets electronically to track beliefs identified. These will be monitored, in addition to the recorded sessions, during ongoing supervision.

PI Allan will train the project staff in coordination with Co-Is Ashrafioun and Stecker. Dr. Allan will train the Project Coordinator to track recruitment and retention as well as data fidelity. Dr. Allan will supervise and train the Project Coordinator to address IRB and grant-related documentation and to monitor the data stream from the mobile app and contact participants as-needed when compliance issues for completion of surveys via mobile app arise.

Therapists with at least a master's degree in a counseling/health-related field and prior CBT experience will deliver BEAST. Drs. Allan and Stecker will train the therapists using the PowerPoint slide deck. Initial training will consist of lecture, role play "rehearsal" techniques, and coding of pre-recorded practice sessions for delivery of intervention content. Ongoing supervision will also be provided by Drs. Allan and Stecker throughout the study. Treatment fidelity will be monitored by recording all intervention sessions, having research assistants code each session for fidelity, and reviewing these tapes and sheets in weekly supervision practice. Adherence scores will be given by transforming the total number of points into a percentage of content delivered. Based on existing measures, we will measure quality of intervention delivery by: (1) Pacing/focus, (2) Communication skills, (3) Therapeutic skills, and (4) Flexibility/Tailoring/Continuity. Each item will be rated on a 5-point Likert scale by the research team. Coding team members will be assigned independent rating of sessions with a 20% overlap of sessions as well as randomly reinserting previously coded sessions to continue to assess interrater reliability.[6,7] Consensus meetings will be held for all double-coded sessions. Interrater reliability (κ) below at least moderate levels, in the overlapping sessions and/or for previously coded sessions will result in immediate retraining of all coders until κ suggests substantial agreement. Coders who continue to perform poorly will be replaced.[8]

Weekly meetings will be conducted to focus on monitoring: a) recruitment, b) conducting interviews, c) coding interview data, d) communication between research staff, e) retention; f) completeness of documentation, and g) storing and safeguarding data.

5.0 Study Procedures

5.1 Study Design

Aim 1 Study Design

Study sample and Screening: We will recruit 6 therapists with experience in telehealth and CBT treatment of Veterans with anxiety and 6 Veterans who meet study eligibility for Aim 2 through the Canandaigua, NY VA.

Assessments and Intervention: Stakeholders (masters-level or higher therapists and Veterans meeting eligibility criteria) will be enrolled following consent. Separate consent forms have been developed for the initial session and the second session. The framework for BEAST exists and will be refined based on feedback received from stakeholders. BEAST comprises two components: face-to-face virtual sessions delivered via telehealth and EMI based on the skills acquired in session, delivered via mobile app. Stakeholders will be asked a series of open- and close-ended questions about the intervention (see Appendix) using an evidence-based expert consensus method for refining the intervention and tailoring the protocol for Veterans. Stakeholders will evaluate the final product after we have completed the one-arm trial and compiled and organized the exit interview information. Final modifications will be incorporated again through seeking consensus with stakeholders.

The study team will work with the Center for Mobile Applications Research Resources & Services (CMARRS) to refine the mobile app and therapist dashboard that will be used to deliver the EMA/EMI components of the intervention. The initial development will occur with the study team using the Mobile App Rating Scale, a multi-dimensional scale assessing an apps engagement, functionality, aesthetics, information, and subjective quality as well as items assessing the perceived impact of the app on the target audience's knowledge, attitudes, intentions to change and likelihood of changing.[40] Ratings across scales range from 1 ("inadequate") to 5 ("excellent"). We will proceed with our app once it receives consensus scores of 4 or higher across all scales among the study team. In the unlikely event that consensus ratings are not achieved, we will resolve through a study team meeting and a simple majority being used to select consensus.

Veteran participants will receive compensation for their participation in the study. The compensation amount will be based on the following:

Prior to Pilot Study	$50
Completion of Pilot Study	$50

Payments will be made via direct deposit, check, or debit card following each study procedure listed above. Participants who do not complete the entire study for any reason will receive compensation for the components that were completed per the above schedule of payments.

VA Clinicians recruited for Aim 1 will not be compensated, instead providing their effort in kind.

Aim 2 Design

Study Sample and Screening: We will recruit 15 Veterans with elevated anxiety sensitivity (i.e.,SSASI ≥ 9) and moderate or higher functional impairment (12-item World Health Organization Disability Assessment Schedule 2.0 ≥ 5[9]). Additional criteria include English-speaking and 18 years of age or older. Veterans do not need to meet diagnostic criteria for an anxiety disorder to benefit from BEAST and therefore the presence of an anxiety disorder is not an inclusionary criterion. Further, because BEAST targets a construct that is non-overlapping with constructs targeted in traditional CBT, Veterans are eligible regardless of current treatment status. The Project Coordinator will conduct all screening and assessments by phone or video call following a script. Potential participants will provide verbal consent to complete the screening measures. Veterans meeting eligibility and interested in participating will be scheduled for a consent and baseline assessment appointment.

Assessments and Intervention: Veterans will be enrolled following informed consent. Veterans will next complete the baseline assessment. At the baseline assessment, Veterans meet with the Project Coordinator by phone or virtually to complete a consenting process, guidance on the video software being used, and set-up and guidance of the mobile app. Research team member will reach out to the Veteran the following day to address any issues with using the app. Veteran will complete assessment surveys for approximately 1 week. At the baseline appointment, participants will be scheduled to receive the face-to-face virtual intervention followed by two weeks of EMA/EMI via mPRO. At the end of the two weeks, Veterans will complete a post-intervention assessment appointment. Follow-up assessment appointments will be completed at the 1-month and 3-month follow-ups. The post-intervention assessment includes an exit interview for participants to provide additional feedback regarding acceptability of the intervention. The research staff will read the measures to the Veteran who will verbally provide their answers; we have found this improves data reliability and completeness immensely compared to mailing packets/sending survey links.

BEAST contains two components: First, there is a single session **face-to-face virtual intervention** delivered by the counselor or therapist, delivered via VA Video Connect software. Second, a **mobile app (mPRO) is used for EMA and to deliver EMI components**.

Face-to-face session. The face-to-face session is a one-hour manualized intervention that uses interactive content to enhance participant learning of critical intervention components. The session includes 1) psychoeducation regarding the role of anxiety sensitivity in exacerbating anxiety sensations, 2) practice identifying and challenging maladaptive thoughts about anxiety, and 3) an IE activity. Psychoeducation is first provided, focusing on the body's alarm system with a goal of normalizing bodily sensations associated with anxiety. Following psychoeducation, the participant and therapist discuss sensations the participant experiences when they are anxious and the thoughts about these sensations that serve to maintain them. The participant and therapist explore challenges to any strongly held beliefs about the danger of anxiety sensations. Finally, the IE consists of: repeated trials of hyperventilation given evidence that this challenge is among the most anxiety-provoking for individuals with panic disorder and our experience using this IE exercise in prior RCTs,[10–12] as well as repeated trials of another selected interoceptive exposure activity. To aid in personalization, Veterans assist in choosing 3 **key takeaways** that summarize what they learned from the intervention regarding anxiety sensations as benign. Common summaries from past participants include: *Anxiety sucks, but it is harmless; I've been anxious before, no big deal!* These summary phrases are incorporated into the EMI. Participants are also asked to complete one set of IE exercises daily for the next two weeks.

EMA. EMA will be collected from baseline to post-intervention and for one week after completing each follow-up. This measurement burst design allows for ratings of functional impairment and anxiety to be calculated disambiguated from state level influences. In our future RCT, this will provide additional power to explore the mechanisms at play. Consistent with best-practice recommendations[13] we will employ a mixture of *fixed time-based sampling, experience sampling*, and *event-based sampling* strategies. In the morning, participants will receive a fixed time-based survey that will include a short battery of questions that will take approximately 2

minutes to complete. Experience sampling will be used to deliver three surveys, distributed quasi-randomly over the remainder of the day (each take 30s to 1 minute to complete). Pulses are randomized such that they are never less than 3 hours and never more than 8 hours apart. Finally, event-based sampling will be used for tracking IE exercise completion.

5.2 Recruitment Methods

Aim 1 Recruitment and retention procedure for Clinical Psychologists: We aim to recruit 6 VA clinical psychologists who self-report experience in CBT, anxiety, and in treating Veterans. We will recruit through emails to colleagues who work with VA clinical psychologists.

Recruitment and retention procedure for Veterans (Aims 1 & 2): We aim to recruit 6 eligible Veterans for Aim 1 and 15 eligible Veterans for Aim 2 from the Canandaigua VA. A two-pronged recruitment strategy will be employed: 1) VA healthcare providers will be able to refer potentially eligible participants by placing the investigators as additional signers on notes using the VA's electronic medical record. To facilitate recruitment, we will present on the intervention at staffing meetings held at various clinics. 2) Veterans with anxiety disorder diagnoses, identified using ICD codes, who are enrolled at the study site will be identified using structured queries of VA administrative datasets. Potential participants will be mailed a personalized letter describing the study and providing a toll-free number so that they can contact study staff if they are interested in participating as well as opt out of future contact. A study flyer will be included with this letter. There will be a QR code on this flyer directing participants toward our screener on Qualtrics that potential participants can complete instead of contacting study staff. We will use several procedures known to promote retention in longitudinal studies.[1-4]

Web-based study screening:

One mode for determining study eligibility will be Qualtrics (www.qualtrics.com), a web-based survey platform. Qualtrics is a popular tool for collecting survey data online with the ability to implement sophisticated study designs. People interested in completing the screening form via Qualtrics will scan the QR code on the flyer which will direct participants to several brief screening questions to ascertain study eligibility, made up of IRB-approved study measures. If eligible and interested, participants can request to be contacted by study staff. All respondents are encouraged to call the toll-free number with any questions/comments /concerns prior to enrolling in the study.

Screening Data. Participants will be asked several questions to confirm eligibility and asked to answer several multiple-choice questions in Qualtrics (or by phone). The information will be stored separately from study data in a password-protected database. Data will be encrypted and stored behind the VA firewall. To enhance data security, access to study data will be limited to IRB approved study personnel. None of these data will be linked to research data.

Self-Report Survey. Data collected for this project will be obtained by online survey. No identifiable data will be included in the limited data set, and a unique identifier will be assigned to each of the records to be used for analysis. Data will then be encrypted stored behind the VA firewall for cleaning and analysis in VINCI. To enhance data security, access to study data will be limited to IRB approved study personnel.

Any recruitment, screening, or payment-related documents will be stored separately (in 'access restricted' file) from study data when received by VA behind VA firewall.

5.3 Informed Consent Procedures

There are three phases where informed consent could be obtained, when stakeholders are reviewing the intervention (Aim 1), when completing the screening for eligibility and when enrolling into the study following the screening and if eligibility criteria are met (Aim 2). Verbal consent to participate will be obtained for all participants. Informed consent will be obtained by study personnel trained in human subjects' protections requirements and how to obtain and document informed consent. Further, questions are embedded at the end of the consent form requiring potential participants to demonstrate comprehension of what they are being asked to do.

5.4 Inclusion/Exclusion Criteria

Aim 1 Eligibility Criteria
Eligibility Criteria for 6 Veterans:

Inclusion criteria: Participants will include men and women Veterans who:

- Are English-speaking
- Are 18 years of age or older
- Score ≥ 9 on the SSASI indicating elevated anxiety sensitivity
- Score ≥ 5 on the 12-Item WHODAS 2.0

Exclusion criteria: **Veterans** will be excluded on the basis of:

- Veterans with cognitive impairment as measured scoring ≥ 11 on the Blessed Orientation-Memory-Concentration Test
- Veterans without access to a smartphone
- Veterans with significant medical or psychiatric conditions that may limit participation, including severe documented schizophrenia, an ongoing active psychotic or manic state, or an imminent suicide crisis will be excluded from our study and provided the appropriate referral.

Eligibility Criteria for 6 therapists
Inclusion criteria: Participants will include masters-level or higher therapists who:

- Are English-speaking
- Are 18 years of age or older
- Report experience in telehealth
- Report experience in CBT treatment of Veterans with anxiety

Aim 2 Eligibility Criteria:

Inclusion criteria: Participants will include men and women Veterans who:

- Are English-speaking
- Are 18 years of age or older

- Score ≥ 9 on the SSASI indicating elevated anxiety sensitivity
- Score ≥ 5 on the 12-Item WHODAS 2.0[9]

Exclusion criteria: Veterans will be excluded on the basis of:

- Veterans with cognitive impairment as measured scoring ≥ 11 on the Blessed Orientation-Memory-Concentration Test[14,43]
- Veterans without access to a smartphone
- Veterans with significant medical or psychiatric conditions that may limit participation, including severe documented schizophrenia, an ongoing active psychotic or manic state, or an imminent suicide crisis will be excluded from our study and provided the appropriate referral.

Pregnant women will not be excluded from this study as no invasive medical procedures are being performed and there is no known risk to the mother or the fetus of the proposed interventions. The study will not include prisoners or institutionalized veterans.

5.5 Study Evaluations

Consistent with recommendations for determining acceptability and feasibility in the context of intervention development, multiple program aspects will be evaluated with the aim of refining BEAST for larger-scale implementation.[15–17] Feasibility of BEAST will be indexed via participant retention, average homework completion, and percentage of EMA sessions completed. Acceptability will be measured using an adaptation of the Program Satisfaction Questionnaire (PSQ), a 14-item measure that assesses both general program satisfaction (usefulness, acceptability) and perceived utility of program components (psychoeducation, EMA/EMI schedule).[18] Measures selected were well-validated, have been administered to Veterans, and/or have been administered via telehealth.

Assessments completed via research staff:

Program Satisfaction Questionnaire (PSQ). Acceptability will be measured using an adaptation of the PSQ, a 14-item measure that assesses both general program satisfaction (usefulness, acceptability) and perceived utility of program components (psychoeducation, EMA/EMI schedule).[18]

Blessed Orientation-Memory-Concentration Test (BOMC). The BOMC will be used to screen for cognitive impairment (i.e., ≥ 11). [19]

Short Scale Anxiety Sensitivity Index (SSASI).[20] The SSASI is a 5-item self-report measure assessing fear of negative consequences of anxiety-related symptoms. Scores ≥ 9 on the SSASI are eligible.

The Anxiety Sensitivity Index-3 (ASI-3).[21] The ASI-3 is an 18-item self-report measure assessing fear of negative consequences of anxiety-related symptoms.

The Intolerance of Uncertainty Scale-12 (IUS-12).[22] The IUS-12 is a 12-item self-report measure assessing fear of uncertainty.

12-Item World Health Organization Disability Assessment Schedule (WHODAS) 2.0. The 12-item version of the WHODAS 2.0 assesses functional impairment across six domains: 1) understanding and communication, 2) self-care, 3) mobility, 4) interpersonal relationships, 5) work and household roles, and 6) community and civic roles.[23]

PROMIS Profile-29[24]. Used to assess the following domains: anxiety, depression, physical function, fatigue, sleep disturbance, ability to participate in social roles and activities, and pain interference.

Functional Impairment Due to COVID (FIDC).[25] A 7-item measure adapted from the WHODAS 2.0 to capture difficulties in functioning due to the COVID-19 pandemic, developed and validated by PI Allan and colleagues.

COVID-19 Impact Battery (CIB) Worries.[25] An 11-item scale measuring distress and worry due to the COVID-19 pandemic.

COVID-19 Impact Battery (CIB) Behaviors.[25] A 12-item scale assessing avoidance behaviors in relation to the COVID-19 pandemic.

Depressive Symptom Index – Suicidality Subscale (DSI-SS). A 4-item measure assessing suicidality within the previous two weeks.

Demographics. At screening, we will assess participants' gender, age, educational background, employment, income, race, ethnicity, marital status, and socioeconomic status.

Exit Interview. The exit interview will assess overall impressions, impact of treatment, relationship with the therapist, and ways to improve the treatment. Acceptability will be measured using an 11-item adaptation of the Program Satisfaction Questionnaire (PSQ) that assesses both general program satisfaction (usefulness, acceptability) and perceived utility of program components (psychoeducation, EMA/EMI schedule).[18] The exit interview and PSQ will inform further refinement of the intervention as needed with our stakeholders. The exit interview will also consist of a number of open ended questions, including prompts to ask for more information, to collect worthwhile feedback on the study procedures, intervention, and their overall feelings toward the intervention.

EMA Measures:

State Short Scale Anxiety Sensitivity Inventory; SSASI[20]: measures anxiety sensitivity.

State Penn State Worry Questionnaire; PSWQ[51]: measures anxious apprehension.

State Anxiety Depression Distress Inventory-27; ADDI-27: measures anxious arousal

The PSWQ and ADDI-27 have been validated as measures of general anxious apprehension and anxious arousal, respectively, reflecting the two core anxiety dimensions underlying anxiety disorders.[26,27] Participants will also rate their impairment across functional domains using the

12-item WHODAS 2.0. Visual analog scale (VAS) ratings from 1-100 will be used to assess anxiety, stress, and depression four times daily. ASI-3 items, revised to capture in-the-moment beliefs, will also be completed. Three items will be randomly selected from an ideographically developed pool of items the participant rates as impacting them “much” or “very much.” Thus, the pool of items to be drawn to potentially deliver EMI will differ by individual.

5.6 Schedule of Assessments

Participants will complete virtual baseline, post-intervention, and 1- and 3-month followups. Participants will receive compensation for their participation in the study but not for the intervention session. The compensation amount and sessions attended will be based on the following:

Baseline Assessment	$40
Face-to-face session	NA
Post-Intervention Assessment	$40
1-month Assessment	$30
3-month Assessment	$30
Weekly EMA Data Collection	$30 per week
≥ 80% of EMA Weekly Surveys	$10 per week

Therefore, the total compensation for completing all the study components would be $340. Payments will be made following each study procedure listed above. Participants who do not complete the entire study for any reason, will receive compensation for the components that were completed per the above schedule of payments.

5.7 Data Analysis

General. To enhance methodological rigor and to allow for accurate dissemination of our findings, we will follow CONSORT guidelines in the design, analysis, and reporting of this study.

Data Management. Dr. Allan, with the assistance of Drs. Ashrafioun and Stecker, will supervise data management using the following services: Enrollment, randomization, tracking of interviews, and auditing of data. A single enrollment and randomization document will be developed to assign identification codes to participants during the pre-enrollment period to track their eligibility status, and randomly assign participants. Similar to our prior studies, a tracking system will be developed to assist research personnel in managing follow-up interviews. This information will be covered during weekly staffing meetings involving Drs. Allan, Stecker, and Ashrafioun as well as the research personnel. Data will be audited for: a) data quality control (% of scales returned for corrections after auditing); b) rate of data entry; and c) backlog of data that has not been entered. All scales will be audited for identifiers, item completeness, and consistency of major clinical indicators. We will store and manage data at the VA with access limited to pertinent study personnel. During the study, we will maintain a dialogue on the technical integrity of our procedures and on conceptual aspects of our project.

Data analysis for Aim 1: *Develop expert consensus for our intervention components using a modified Delphi method.* Specifically, a modified Delphi Method will facilitate the incorporation of expert and stakeholder feedback to reach consensus.[38,39] We will present to our stakeholders the results of our study and any proposed changes as-needed after we complete Aim 2 (one-arm trial). Experts and stakeholders will rate each component as: a) acceptable as is, b)

acceptable with minor changes, or c) unacceptable. For each component, our intervention will be considered ready for Aim 2 if at least 4 of 6 clinicians and 4 of 6 veterans meeting eligibility criteria rate it to be acceptable as is and two rate it as acceptable with changes. If any member rates the content as unacceptable, we will meet with these participants individually to discuss why they rated the intervention as such. Experts and stakeholders will again evaluate any component of the intervention that did not meet eligibility criteria after the initial round of review. determine if the change would invalidate the intervention. If so, the team will agree not to make the suggested change. Correspondence with the expert panel will be done via email and virtual meetings. A final meeting regarding the summarized findings from the second round of feedback will be held by the investigative team to finalize the protocol. We will meet with our stakeholders to resolve any disagreements between the investigative team and our stakeholders.

Data analysis for Aim 2: *Assess the feasibility, acceptability, and usability of BEAST***.** We will track the number of Veterans who are recruited per month. We will calculate the percentage of participants who complete the protocol and follow-ups to calculate acceptability. Treatment acceptability will be assessed with the exit interview. Therapist fidelity scores for the individual session will be assessed as the percentage of the content delivered. Interrater reliability for fidelity and competence will be assessed using intraclass correlation coefficients. When incorporating information from the exit interview, raters will provide perspectives, discuss their summarized responses, and reach consensus on different factors (e.g., format, receptivity, feasibility).

The PI will check the work of the raters and chart the data to further examine the domains, core ideas, and categories that describe the themes. Means and standard deviations for outcomes will be calculated at each assessment, including change scores and correlations across timepoints. We expect large standard errors due to sample size. Distribution of scores will be examined to better evaluate how to analyze these data in future studies. For continuous outcomes, Hedge's *g* will be calculated to identify a range of the pre-post effect size. Although such calculations are of limited benefit in determining the effect of the intervention, they are helpful in identifying outcomes for which the intervention may be less effective.

For data quality and handling of missing data, descriptive statistics will help identify out of range values and outliers. *The assessment battery* will be considered acceptable if no questionnaires are missing in full in more than 25% of the participants and if reliability is higher than 0.70. *Acceptability of EMA procedures* will be assessed through calculating the percentage of EMA surveys completed as well as completion patterns. BEAST will also be considered feasible and acceptable if $\geq$ 70% of the EMA sessions are completed by $\geq$ 80% of participants, consistent with prior rates in studies conducted and reviewed by Dr. Allan. Acceptability will also be measured using an adaptation of the PSQ, an 11-item measure that assesses both general program satisfaction (usefulness, acceptability) and perceived utility of program components (face-to-face sessions, EMA/EMI).[18] Finally, an average PSQ general satisfaction score of $\geq$ 4 (on a 5-point scale) and an average PSQ mobile app score $\geq$ 4 (on a 5-point scale) will provide support for the feasibility and acceptability of BEAST. The research team and stakeholders will

meet and discuss the intervention regarding benchmarks of acceptability and feasibility as well as the information gathered during the exit interviews.

Power analysis. As this is a pilot trial, we did not conduct a formal power analysis when selecting the sample size. Rather, we used stepped rules of thumb to optimize the overall sample size for the pilot and main effects study.[28] Based on these stepped rules of thumb and an expectation of clinical effect sizes in the medium range on primary and secondary outcomes of the RCT, 15 participants is considered adequate.

Future trial. Findings from this pilot trial will provide the necessary infrastructure and demonstration of feasibility to allow us to expeditiously conduct a fully powered RCT and then disseminate through the VA. At the completion of this study, we will have refined the treatment manual, the mobile app design and schedule, and the study protocol/pipeline. Therefore, it is expected we will be well-positioned to pursue a MERIT award to provide evidence of efficacy of BEAST.

Data storage, security, and confidentiality. Several procedures for protecting participant confidentiality will be implemented to reduce the risk of revealing participant identity. All informed consent forms will contain identifying information. To ensure confidentiality, each consent form will be labeled with a numeric identifier and will be stored in a double-locked file. These will be stored in separate double-locked files from other study materials.

The VA Informatics and Computing Infrastructure (VINCI) will be used for the storage of study data. VINCI is a major informatics initiative of the Department of Veterans Affairs (VA) that provides a secure, central analytic platform for performing research and supporting clinical operations activities. It is a partnership between the VA Office of Information Technology (OI&T) and the Veterans Health Administration Office of Research and Development (VHA ORD). VINCI includes a cluster of servers for securely hosting suites of databases integrated from select national VA data sources. VINCI servers for data, applications. and virtual sessions are physically located at the VA Austin Information Technology Center (AITC), located in Austin, Texas. This secure enclave with 105 high-performance servers and 1.5 petabytes of high-speed data storage has multiple layers of security and disaster recovery to prevent data loss.

Study data will be kept in accordance with the Department of Veterans Affairs Record Control Schedule 10-1 (RCS 10-1). Storage and transfer of any Personally Identifiable Information (PII) or Protected Health Information (PHI) must be done in accordance with applicable VA and VHA policies and directives, state and federal regulations, and applicable statutes including the Health Insurance Portability and Accountability ACT (HIPAA). Unless explicitly requested and approved by data stewards, all sensitive patient data must remain on VINCI project servers and only aggregate data without PII / PHI may be transferred from VINCI. At the completion of the study, disposition of records will also follow guidelines of RCS 10-1 in accordance with VA, VHA, and HIPAA policies and directives as mentioned previously.

Prior to being uploaded to VINCI for analysis, data will be stored on a secure VA server, which is password protected, and to which only IRB approved VA research personnel have access. Should any identifiable information need to be shared between research sites, research teams

will utilize a secure, SharePoint site or electronic communication with PKI encryption. Any identifiable paper data will be stored in two separate locked file cabinets (one for informed consents and the other for paper questionnaire data) in the offices of the Center for Excellence for Suicide Prevention at the Canandaigua VAMC and VA Center for Integrated Healthcare at the Buffalo VAMC. After a participant completes the study, any identifiers will be removed from the paper questionnaire data immediately. Data analysis will occur in the VINCI framework.

5.8 Withdrawal of Subjects

Participants who wish to withdraw may do so at any time without affecting their medical care or participation in any other study. Participants will be informed of any new information throughout the duration of the study which may affect their condition or influence their willingness to continue in this study. Finally, based on decisions made by the Principal Investigator, participants may be taken out of the study because of unanticipated circumstances such as extreme distress. That is, they may be withdrawn from the study if we judge that participating is not in their best interest.

6.0 Protection of Human Subjects

Human Subjects Involvement and Characteristics. The purpose of this study is to assess the acceptability, feasibility, and usability of an intervention designed to reduce anxiety sensitivity and functional impairment among Veterans with elevated anxiety sensitivity experiencing functional impairment. A total of 15 participants will be recruited through the Canandaigua VA and receive Brief Enhanced Anxiety Sensitivity Treatment (BEAST) through telehealth and supplemented via a mobile app.

Source of Materials. Study materials will include self-report questionnaires. The materials will be collected for study purposes only. Information collected will be stored in a locked filing cabinet in a locked office at the study sites that can only be accessed by members of the study team. *All electronic data* will be stored on VINCI project servers. Only approved study team personnel who will be involved in data entry, management and analyses will be granted access to this data. All computers are password protected.

Recruitment and Informed Consent.
All research staff conducting recruitment and informed consent will have completed appropriate and up-to-date training in research, research ethics and the proper conduct of research that includes common issues related to recruitment and informed consent.

Veterans will be identified using structured queries of VA administrative datasets. Research staff will use these lists to identify potentially eligible participants and to enhance the number of Veterans at high risk, women and/or minorities recruited into the study. Research staff will mail an IRB-approved letter describing the study to the Veteran. Research staff will call all patients who receive a letter unless the patients call a number to opt out. These are Syracuse VA IRB-approved procedures that are used by researchers at the Center of Excellence for Suicide Prevention and Syracuse VAMC. There is no more than minimal risk to the participants and the rights of the participants, or their welfare, will not be adversely affected. Recruitment and informed consent procedures were designed to ensure patients do not feel like participation is required. Patients unable to understand the informed consent process will be excluded from participating. Screening interviews will be completed initially over the telephone (using a script)

to assess eligibility criteria. Verbal consent will be obtained at this time to complete the screening. Participants screening positive for exclusion criteria will not be included in the study. Veterans who report suicidal intent with a plan will be transferred to the Veteran's Crisis Line (as detailed below in Protection Against Risk). For eligible and interested participants, a research assistant will review the consent form and complete a brief questionnaire to ensure the potential participant understands the study.

Participants will receive compensation for their participation in the study due to the time commitment required. The compensation amount will be based on the schedule that follows per aim, also found earlier in this protocol:

Aim 1:

Prior to Pilot Study	$50
Completion of Pilot Study	$50

Stakeholders will be provided compensation prior to the pilot study when feedback is given, as well as after the pilot study has been completed for a total of $100 as compensation for their time.

Aim 2:

Baseline Assessment	$40
Post-Intervention Assessment	$40
1-month Assessment	$30
3-month Assessment	$30
Weekly EMA Data Collection	$30 per week
$\geq$ 80% of EMA Weekly Surveys	$10 per week

Therefore, the total compensation for completing all the Aim 2 study components would be $340. Payments will be made following each study procedure listed above. Participants who do not complete the entire study for any reason, will receive compensation for the components that were completed per the above schedule of payments.

Protection Against Risk.
Anticipated risks to the participants from assessment procedures and therapy are minimal; however, participants may experience psychological distress, frustration, and/or fatigue. The semi-structured interviews, assessments associated with the intervention, and therapy sessions encourage participants to recall personal events and life stressors that may evoke distress. Participants will be told they can withdraw from the study at any time. Participation or withdrawal from the study will not affect any benefits to which they are otherwise entitled. Special precaution will be taken to safeguard confidentiality.

All assessors and interventionists will have a specific protocol to follow regarding emergency care and will have the clinical back-up of Drs. Allan, Stecker, and Ashrafioun. This study will use safety procedures that have been previously approved by the IRB in several of our protocols. All research staff will be thoroughly trained on these procedures. These include written procedures for handling emergencies, a written procedure for conducting a full suicide risk assessment whenever suicidality is endorsed, procedures for participants endorsing a suicidal plan or intent (including staying with a patient until they are connected with a mental health provider or 911

help), and a written warm-handoff guideline to connect Veterans to the National Veterans/Military Crisis Line (VCL).

In any of the above instances, the research staff member will read (or paraphrase) the following statement to the participant at the end of the call:

> *I am concerned about your safety and so at this time I am going to transfer you to speak with one of our mental health clinicians at the Veterans/Military Crisis Line. There will be a moment of silence as I connect you. If for some reason we get disconnected please dial 1-800-273-8255 and press #1 to reach the Lifeline. I will stay on the line with you until the transfer is complete. I am now going to transfer you. Please stay on the line.*

The researcher will briefly summarize the participant's situation to orient the VCL responder to the nature of the call (the participant will hear a moment of silence at this time, and then the participant will be transferred to the VCL).

If the participant hangs up or becomes disconnected, the researcher will call the VCL immediately, and the VCL staff will take necessary actions as appropriate according to the VCL safety protocol and/or direct the researcher what actions to take. These actions may include initiating a "rescue" that involves calling 911 at the participant's local jurisdiction and having emergency personnel come to the participant's home to ensure their safety. The VCL staff performs rescues every day, and all rescues are done in collaboration with a supervisor. We have ongoing collaborations with the VCL and have substantial experience working with responders and supervisors. Our approach to participant safety will be applied to all participants including control participants and is guided by ongoing clinical and research experience in suicide prevention, including our Center Director's affiliation with the VCL.

We will collaborate closely with the VCL during the study start-up phase to review these safety protocol steps. As a reminder, the VCL, which was established in 2007 at the Canandaigua VAMC, can be reached anytime by calling 1-800-273-8255. The VCL has grown to be one of the largest in the world, with a full-time staff of more than 600 full-time responders. VCL responders are paid professional staff and nearly all have a Master's degree in a relevant field (e.g., mental health counseling), distinguishing the VCL from others in the U.S. that are staffed primarily with volunteers.

VCL resources will be available as back-up at all times during study sessions. VCL responders are arguably the foremost experts in managing acute suicidal crises via telephone. They have in place protocols for locating suicidal individuals, identifying the closest police and emergency medical services, and monitoring and documenting "rescues." Moreover, VCL responders have the ability to look up call histories based on callers' phone numbers, a capability that since implemented has greatly aided the ability of responders to rapidly assess callers' needs.

All participants will be provided the VCL phone number at the end of each baseline assessment and at each follow-up assessment and encouraged to call the number should they become suicidal, simply wish to talk with someone, or would like assistance in obtaining a referral for mental health treatment. In situations in which potential suicide risk is identified during a phone call, we plan to use two levels of response: 1) researcher transfers the individual to the VCL (used in acute crises requiring emergency intervention or "rescue"); 2) researcher offers the participant a transfer to the VCL, but does not perform the transfer if he/she does not wish to be transferred (used in non-emergency situations).

Breach of Confidentiality. Statistical data files will be kept on VINCI project servers maintained by VINCI OI&T personnel and only summarized data without protected health information (PHI) will be downloaded from VINCI to local storage media. Research staff will use an audited VINCI download utility to move summarized data for reports, presentations and publications from VINCI servers to local storage media. The VINCI download utility provides an audit path including a copy of the downloaded material. The data extraction tool will be adapted for use with software directly available on the VINCI platform (e.g. Microsoft Word and Excel) and study data will be stored and maintained on VINCI. All study team personnel with access to sensitive patient data will stay current on their VA approved information security training and VA approved privacy policy training.

Adverse Events (AE). All research staff will participate in an intensive training to help them understand the importance of reducing the risk for participants and learning how to recognize and report any AE or SAE. AEs may include, but are not limited to: worsened physical or mental health, or inadvertent disclosure of confidential research information. Serious Adverse Events (SAE) may include: death, hospitalization due to worsening psychiatric symptoms or suicidal ideation, or all life threatening or disabling/incapacitating events among research participants. Per IRB regulations, SAEs, any event resulting in a deviation from the study protocol (e.g., emergency hospitalization to address suicidal behaviors) or death will be reported to the PI within 24 hours and to the IRB in 48 hours. He will make a decision whether there is sufficient evidence to suspend data collection, allow for further IRB review, modify the protocol, or make other changes to reduce potential risk to participants. The study will resume based on agreement of the PI, and an IRB member (the chair will recuse himself because he is a co-I on the study). Immediate evaluation will occur to determine if any extra steps can be taken to minimize the likelihood of that type of AE occurring again. If changes can be made, a report/amendment will be written and submitted to the IRB. AEs that involve temporary distress will be noted by interviewers and provided to the IRB in an annual report.

Confidentiality of Records: Numerous protections are in place to reduce the likelihood of loss of confidentiality. All research data will be kept in locked filing cabinets in secure areas, absent of identifying information, and coded by research number only. Files containing consent forms and other items with identifying information will also be kept in locked filing cabinets, but these will be separate from cabinets containing data from this study. Social security numbers (SSNs) may be collected based on the participant's preferred payment methods. These SSNs would only be used as part of fiscal forms needed for payment, and these payment vouchers would be stored within protected electronic folders for documentation purposes only.

Potential Benefits of Research to Participants and Others. There may be direct and/or indirect benefits of study participation. Participants may benefit from receiving the intervention as it is designed to reduce sensitivity to anxiety. Participation in this intervention will benefit future Veterans as we can identify if these interventions can reduce anxiety and improve functional impairment in Veterans experiencing elevated anxiety sensitivity. Dissemination of the findings from the study will contribute to the extant literature and will inform future implementation efforts.

Importance of Knowledge to be Gained. This study is important to science and society because there is an urgent need for brief interventions to help individuals that experience anxiety and anxiety sensitivity. This study represents an important step towards making these interventions more accessible. Ultimately, this intervention could be an efficient means to reduce anxiety in Veterans.

Data Safety & Monitoring Plan

Data Safety. To ensure safety of participants in the study proposed and validity and integrity of data collected, the PI (Allan) will oversee all data and safety monitoring functions and the research team will be advised that he will be the primary contact overseeing these activities. The investigators will meet regularly to monitor study progress and discuss the implementation of monitoring procedures. The PI will also meet regularly with the research coordinator and staff to review monitoring procedures and ensure all efforts are being taken to minimize risks to participants. As indicated above, the PI will track all negative outcomes and incidents as well as conduct interim data analysis every 12 months after the study has started. The study design will be significantly modified if the study is creating potential harm to our participants.

The PI and Dr. Stecker will regularly oversee all aspects of the study, including participant recruitment, informed consent, data collection, management, and analysis, as well as regularly assess the risk/benefit ratio associated with participation in the study.

As part of a standard practice, the PI will supervise the implementation of one audit within 4 months after study recruitment and one regularly per year afterwards of the materials collected and produced as part of the study at each site to ensure proper confidentiality and compliance with ethical principles, including informed consents, questionnaire data, and to make sure that the research staff are following established protocols. The PI will provide an annual summary report of all AEs to the IRB as part of the annual review. If no adverse events have occurred, the report will state, “No adverse events affecting human participants have occurred during this project year.”

Data Monitoring. To ensure adequate participant recruitment and enrollment, each week, the PI will discuss the current number of participants contacted, screened, and enrolled from each site and compare those numbers to the expected based on our preliminary data. If after the first 4 months, it appears we are not reaching our expected number of participants, the PI will discuss potential barriers/obstacles and solutions with the research team and we will enact contingency plans as needed.

7.0 References

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