Mobile Intervention for Veterans With PTSD and Anger

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Protocol

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PROTOCOL TITLE: Developing a Mobile Intervention for Veterans with Posttraumatic Stress Disorder and Problematic Anger

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Purpose

The goal of this research is to develop, refine, and pilot-test a mobile application version of an existing computer-based interpretation bias modification (IBM) intervention for individuals with PTSD and problematic anger.

Background and Significance

Difficulty controlling anger is the most commonly reported reintegration concern among combat Veterans (Sayer et al., 2010). In a national survey of 754 Iraq and Afghanistan combat Veterans receiving VA medical care, 57% reported increased difficulty controlling their anger since returning from deployment (Sayer et al., 2010). Furthermore, among Veterans with PTSD, anger difficulties are significantly more prevalent. For example, in the same study cited above, among those with probable PTSD, the endorsement of anger difficulties increased to 84%. Anger difficulties are consistently strongly associated with PTSD (Olatunji et al., 2010; Orth & Wieland, 2006). Anger predicts PTSD symptom severity (Koenen et al., 2003; Novaco & Chemtob, 2002; Riggs et al., 1992) and responsivity to PTSD treatment is associated with reductions in anger (Cahill et al., 2003; Galovski et al., 2014).

Among Veterans, problematic anger is associated with numerous negative psychosocial outcomes, including discord in family relationships (Galovski & Lyons, 2004; Ray & Vanstone, 2009), aggression (Elbogen et al., 2010; Novaco & Chemtob, 2015; Wilk et al., 2015), road rage (Possis et al., 2014), unemployment (Frueh et al., 1997), and suicide risk (Doran et al., 2017; Nock et al., 2015). In addition to impairing psychosocial functioning, anger can also impede successful outcomes from PTSD treatment. Pre-treatment anger accounts for both higher levels of dropout (Rizvi et al., 2009; Stevenson & Chemtob, 2000) and less PTSD symptom reduction (Foa et al., 1995; Forbes et al., 2003; Speckens et al., 2006; Taylor et al., 2001). These findings highlight the need for increased focus on improving treatments for anger in Veterans with PTSD and the importance of enhancing treatment engagement among this high need group of Veterans.

According to cognitive models of anger, individuals with problematic anger have a tendency to interpret ambiguous interpersonal situations as hostile (Wilkowski & Robinson, 2008; 2010). For example, if someone bumps into them in a crowd they may be more likely to interpret this as an aggressive action than a mistake (Wilkowski & Robinson, 2010). In fact, *hostile interpretation* of situations has been identified as the first step in the elicitation of anger and subsequent aggression in multiple models of anger and aggression (Bond et al., 2004; Dodge, 1980; Epps & Kendall, 1995; Hazebroek et al., 2001; Wenzel & Lystad, 2005; Wilkowski & Robinson, 2010).

Cognitive-behavioral approaches to anger have primarily targeted hostile interpretation bias with cognitive restructuring (Beck & Fernandez, 1998; Gorenstein et al., 2007). In cognitive restructuring, patients learn to monitor their thoughts, identify those that lead to negative emotions (e.g., anger), evaluate the accuracy and utility of these thoughts, and then to replace unhelpful and extreme thoughts with thoughts that are more balanced and adaptive. Though this cognitive approach is effective (Del Vecchio & O'Leary, 2004), cognitive restructuring is a challenging task with this population. This process takes several sessions to teach (e.g., typically 8 to 12 one-hour sessions) and requires out-of-session practice and monitoring by the patient. Additionally, patients with anger problems may respond resentfully to the suggestion that their interpretations are incorrect (Gorenstein et al., 2007) and may cling to the belief that others (not them) are the sole source of the problem (DiGiuseppe & Tafrate, 2007; Siddle et al., 2003).

Interpretation bias modification (IBM) techniques have been used in recent years to modify maladaptive interpretation biases that are theorized to cause and maintain anxiety and depression (Menne-Lothmann et al., 2014). IBM is delivered *via* computer and essentially helps participants to adopt more adaptive interpretational styles through repeated practice resolving ambiguous situations in a benign way. Mathews and Mackintosh (Mathews & Mackintosh, 2000) conducted the first studies of this kind by experimentally inducing either benign or anxious interpretations to ambiguous events and demonstrating that this interpretation training could alter anxiety in response to a subsequent stressor. Additional studies have used similar methods to effectively reduce symptoms of social anxiety (Amir & Taylor, 2012; Beard & Amir, 2008), generalized anxiety disorder (Hayes et al., 2010), trait anxiety (Mathews et al., 2007), and body dysmorphic disorder (Summers & Cougle, 2016).

Previously, Dr. Dillon and her colleagues have adapted IBM to target hostile interpretation biases in several studies. In the first of these studies, they found that a single-session (lasting about 15 minutes) of IBM effectively reduced hostile interpretation bias and subsequent anger reactivity to an interpersonal insult (Hawkins* & Cougle, 2013; note Hawkins is Dr. Dillon's maiden name). Next, this IBM program was developed into an eight-session intervention, which has been found to be effective at reducing interpretation bias and anger outcomes in two randomized controlled trials, one in a sample of individuals with alcohol use disorder and problematic anger (Cougle et al., 2017) and another in a sample with major depressive disorder and problematic anger (Smith et al., 2018). In both of these studies, the complete intervention took a total of two hours (eight 15-minute sessions) and was delivered entirely *via* computer. In this sense, cognitive bias modification protocols represent more efficient, focused, and less confrontational means of administering cognitive restructuring.

Aims

The *goal of this project* is to develop, refine, and pilot-test a mobile application version of the existing IBM intervention in order to reduce anger and functional impairment among individuals with PTSD and problematic anger. The study will be undertaken with the following aims:

Stage/Aim 1: Refine the *Mobile Anger Reduction Intervention (MARI)* app in two successive cohorts of *n*= 5 Veterans with PTSD and problematic anger. After the first cohort uses the application for a period of four weeks, a qualitative and quantitative evaluation will be conducted and each participant will be interviewed. Revisions will then be made based on these evaluations before another cohort of *n* = 5 Veterans is treated. Again, following treatment an evaluation will be completed and further revisions will be made to the treatment. The resulting iteration of the treatment will be used in the subsequent pilot randomized controlled trial (Aim 2).

Stage/Aim 2: a) Evaluate the feasibility of recruitment, randomization, and retention procedures in a pilot study comparing MARI to a contact control condition (mindfulness app); and b) utilize psychophysiological and electronic diary monitoring to determine whether this assessment could be used as an outcome or mechanistic variable in a subsequent randomized clinical trial application focused on evaluating the efficacy of the MARI intervention. Aims 2a and 2b will be evaluated in a third cohort of 40 individuals with PTSD and self-reported problematic anger that will be randomized in a 1:1 ratio to MARI (*n* = 20) versus the mindfulness control condition (*n* = 20).

Design

The proposed research project is comprised of two stages. Each stage has its own aim. In the first stage (Stage/Aim 1) a successive cohort design (Epstein et al., 2007) will be used to refine the MIRA intervention two cohorts of 5 participants with PTSD and problematic anger. In the next stage (Stage/Aim 2), we will conduct a small, randomized controlled trial of MIRA compared to a mindfulness intervention (matched for time and participant contact) in a third cohort of 40 individuals.

Stage/Aim 1: We propose to recruit two successive cohorts of 5 participants with PTSD and problematic anger. In each cohort, participants will come in to the laboratory for a pre-treatment visit. After establishing that they meet study criteria (including completion of a diagnostic interview to confirm PTSD diagnosis), they will complete some self-report questionnaires, and they will follow a think-aloud protocol (Jääskeläinen, 2010) during their initial use of the MARI intervention. They will then be asked to continue to use the mobile application five times weekly for the next four weeks. At the end of the first week of treatment, participants will be contacted over the phone to check in about whether they have encountered any problems with the app, answer any questions that they have, and remind them to use the app. After completing four weeks of treatment, each participant will return for a post-treatment visit during which they will provide feedback on their experience using the MARI application. These interviews will be audio-recorded. Their satisfaction with the MIRA intervention will be assessed with an in-depth interview about their impressions of the treatment (e.g. treatment dose, timing, and frequency; intervention content; text messaging; procedures). These interviews will ask them questions regarding how helpful they found the intervention and how useful and user-friendly they found the app. They will be asked to elaborate upon what aspects of the intervention and app they think are most and least helpful and to provide suggestions on how it could be improved. Data regarding their use of the application (e.g., frequency of use, timing of use) will also be collected.

Based upon results, the intervention structure and content will be revised. The content that will be subject to revisions includes: the IBM content (e.g., topics and themes of scenarios); the MARI app structure and flow; the dose, timing, and frequency of the treatment sessions; and the methods used to promote treatment engagement and compliance.

After the intervention and study has been modified based on the information learned from the first cohort, we will treat a second cohort (*n* = 5). Again, we will use qualitative and quantitative data to refine that app in preparation for Stage 2 of the project.

Demographics and Background Measures	Time (min)	Pre-treatment	Post-treatment	3-month follow-up
Demographics	2	●		
Traumatic Life Events Questionnaire (TLEQ)	10	●		
Diagnostic Interviews				
Clinician-Administered PTSD Interview, DSM-5	60	●		
Structured Clinical Interview for DSM-5	60	●		
Feasibility and Acceptability Measures				
Participant Recruitment	--	●		
Treatment Retention	--		●	
Withdrawals	--	●	●	●
App Utilization	--		●	
Client Satisfaction Questionnaire (CSQ)	5		●	
Post-treatment Interview	30		●	
Clinical Measures				
Word Sentence Association Paradigm-Hostility (WSAP-H)	10	●	●	●
State Trait Anger Expression Inventory-2 (STAXI-2)	15	●	●	●
Dimensions of Anger Reactions (DAR)	5	●	●	●
Revised Conflict Tactics Scale (CTS2)	5	●	●	●
PTSD Checklist for DSM-5 (PCL-5)	10	●	●	●
Past Week Anger Measure	5	●	●	●
Social Information Processing—Attribution and Emotional Response Questionnaire (SIP-AEQ)	15	●	●	●
Hostile Interpretation Bias Task*	10	●	●	●
Functional Outcome Measures				
WHO-DAS 2.0	20	●	●	●
Brief Inventory of Psychosocial Functioning (IPF)	12	●	●	●
Quality of Life Inventory	5	●	●	●
Work Limitations Questionnaire (WLQ)	10	●	●	●
Couples Satisfaction Index (CSI)	10	●	●	●
Additional Measures				
Credibility and Expectancies Questionnaire	5	●		
Pain Severity Questionnaire	1	●		
Patient Health Questionnaire-9 (PHQ-9)	5	●	●	●
Beck Scale for Suicide Ideation	5	●	●	●
Cognitive Flexibility Inventory	5	●		
Pittsburgh Sleep Quality Index (PSQI)	5	●	●	●

Assessments for Partner, Family Member, or Friend**				
Revised Conflict Tactics Scale (CTS2)	5	●	●	
Couples Satisfaction Index (CSI)	10	●	●	
Dimensions of Anger Reactions (DAR)	5	●	●	

**Hostile Interpretation Bias Task (HIBT):* This assessment will be done on the computer. The HIBT (Smeijers, Rinck, Bulten, van den Heuvel, & Verkes, 2017) is a computerized assessment that involves showing participants photographs of faces and asking them to rate whether the face looks hostile or not, as quickly as possible. The faces have angry, fearful, disgusted, and happy expressions that have been morphed with neutral faces to present faces that are 20%, 40%, 60%, 80%, and 100% intensity of the depicted emotional affect. This task will be done on a computer while the research staff is in the room the entire time that the participant uses the computer.

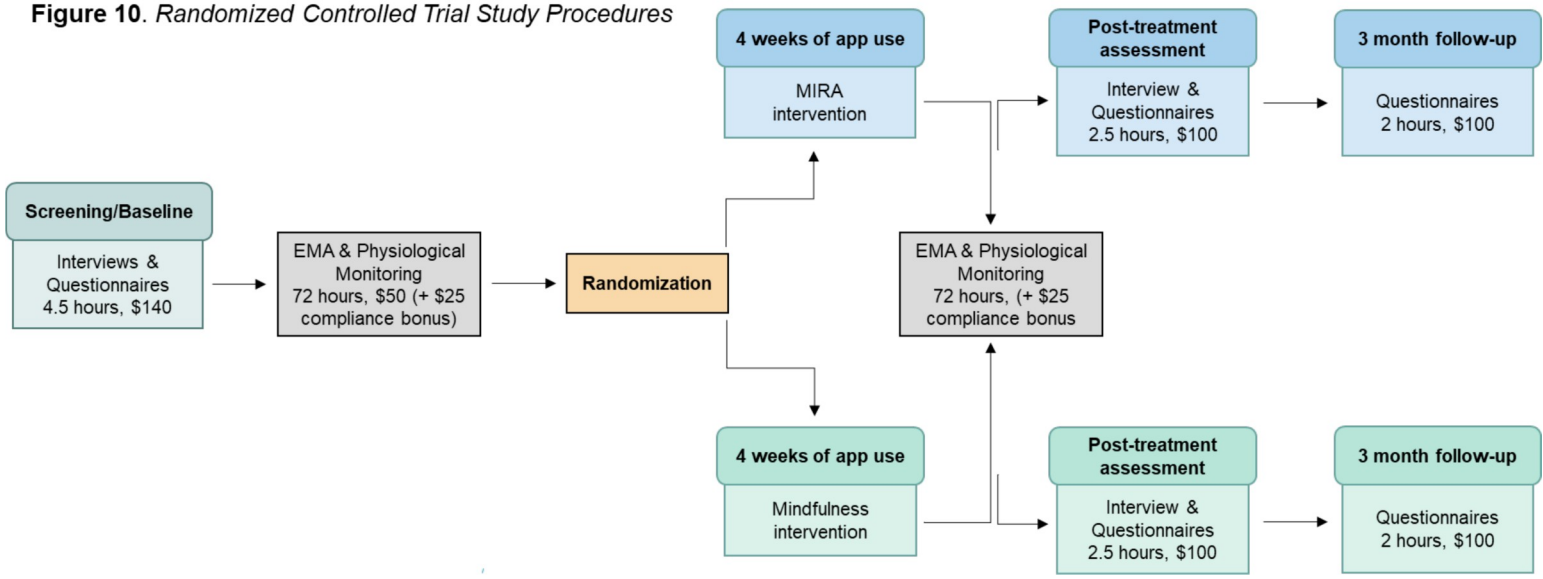
***Assessments for Partner, Family Member, or Friend:*

Revised Conflict Tactics Scale (CTS2): This is a questionnaire that assesses interpersonal aggression. Similarly to other research done by our team (Beckham et al., 1997; Kirby et al., 2012), participants will complete the questionnaire three times using different instructions each time. First, in order to assess interpersonal aggression, they will complete the questionnaire indicating how often they have perpetrated the given aggressive act toward their collateral informant (spouse/partner, close family member, or friend) in the past month. They will also indicate how often the informant has perpetrated the aggressive acts toward themselves. Then, in order to assess general aggression, they will complete the same questionnaire in reference to how often they have engaged in given act to "anyone" in the past month. Spouses/partners will also be asked to complete this measure twice. Once in reference to how often the Veteran has perpetrated each of these acts against them and once in reference to how often they have perpetrated them against the Veteran. They will also be asked to complete the Dimensions of Anger Reactions questionnaire on themselves and on the Veteran. If no spouse or partner is available, then another family member living with the Veteran will be asked to participate. If none are available, the Veteran will be asked to select the family member or friend they interact with most frequently. If participants report that they are in a romantic relationship, the Couples Satisfaction Index (CSI) will be used to assess relationship satisfaction. The participant's spouse or partner will also be asked to complete this questionnaire.

Stage/Aim2: We propose to recruit 40 participants for the second stage of the study. Recruitment procedures and inclusion/exclusion criteria will be the same as those from Stage/Aim 1. After an initial phone screen, interested participants will come in for a pre-treatment assessment. After confirming that they meet study criteria (including completion of a diagnostic interview to confirm PTSD diagnosis), they will complete baseline assessments (see assessment table above). If participants are eligible, they will sign a Duke informed consent form for the mobile health procedures of the study, which include wearing a portable heart rate monitor and using a smart phone for recording information about affect for 72 hours. After this baseline period, they will return the Duke equipment. They will then be randomized to either the MARI or mindfulness control condition (n = 20 per condition). Participants will be shown how to access their assigned intervention via Duke-owned smartphone. At the end of the first

week of treatment, participants will be contacted over the phone to check in about whether they have encountered any problems with the app, answer any questions that they have, and remind them to use the app. They will also complete a short interview about their impressions of the app at that point (see One Week Interview). They will be asked to continue to use the mobile application in the Duke study for the next four weeks. Next, they will do the ambulatory HRV monitor and electronic diary for a period

Figure 10. *Randomized Controlled Trial Study Procedures*



of 72 hours. Then, participants will return for an in-person, post-treatment visit**.** Finally, they will complete a three-month follow-up visit (see Figure 10 below).

Mobile Device Use

Study participants will access the MARI and mindfulness apps using Duke-owned mobile devices and a separate Duke IRB protocol is in place for this part of the study. These data collected with Duke-owned devices will be Duke-owned data, not VA-owned. This Duke-owned data will then be combined with VA data, and transferred via a VA-owned FIPS-encrypted thumbdrive or via VA's S.A.F.E.

Risk/Benefit Assessment

Participation is completely voluntary and participants are informed that they are free to refuse to answer any items on the questionnaires or questions from the interview that they do not wish to answer. They are also informed that they are free to decline participation in any procedure and can withdraw from the study at any time. Regarding qualitative data, participants will be informed that all published results will be anonymized, including any mention of city/medical center/clinic to protect the identity of participants.

Potential risks will be minimized by carefully screening potential participants according to the inclusion/exclusion criteria, closely monitoring symptom levels, and following established laboratory procedures. To ensure confidentiality, all records will be identified by the participant's identification number, not by name. All raw hard copy data will be kept in a locked file cabinet in a locked room. Data files will be stored on secure,

password-protected computers. Finally, all project staff will complete educational units required by the Durham VAHCS IRB.

While participants may benefit from using the mobile intervention, there are no guaranteed benefits to the individual participant and no immediate benefits of the proposed research to others. There are potential benefits to others from the information generated that potentially will be helpful in increasing reach of anger treatments and developing more effective anger interventions for Veterans with PTSD and problematic anger. In our opinion, the anticipated benefits of this study outweigh the potential risks.

Selection of Subjects
We will screen up to 70 participants for the project (both stages) for a desired total sample size of 50. We anticipate that 50 spouses/partners/family members will provide consent to complete questionnaires by telephone.

Inclusion/Exclusion Criteria	
Veterans must meet **all** inclusion criteria:	Veterans who meet **any** one of the exclusion criteria will be excluded: _
• Diagnosed with PTSD, established *via* the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) • Report a score of ≥12 on the 5-item Dimensions of Anger Reactions Scale • Can read at least 6th grade level material	• Expected to be unstable on their medication regimen during the study • Currently in a period of active psychosis or mania • Exhibit current prominent suicidal or homicidal ideation requiring immediate intervention • Receiving (or plan to receive) other anger management psychotherapy or trauma-focused therapy for PTSD (i.e., prolonged exposure, cognitive processing therapy during the course of the study

Subject Recruitment
Participants will be recruited using a Data Access Request Tracker (DART) request to identify Veterans with PTSD diagnoses from Regional and/or Corporate Data Warehouse. Potential participants will be sent an introductory letter that describes the study and informs them that they will be called regarding participation. In the letter, potential participants will be given an “opt-out” number to call in order to decline participation and/or further contact regarding participation. Seven business days after the mailing, Veterans who have not called the toll-free number to decline participation will be contacted by a study team member to request their participation in the research study.

We will also recruit veterans from the Traumatic Stress and Health Laboratory’s “Contact Database,” IRB #1080; this database contains information about previous lab study participants who have agreed to be contacted about other studies for which they may qualify.

Additionally, participants will be recruited from the Mid-Atlantic MIRECC's repository. We will submit a data request to the MIRECC to obtain a list of participants with a current PTSD diagnosis who have enrolled in the repository and agreed to be contacted about future studies.

We will also post recruitment flyers in the Durham community and around the Durham VA hospital and clinics.

Clinicians in clinics throughout the medical center will be provided information about study eligibility and basic procedures (see clinician card and brochure), and will be asked to refer potentially eligible veterans. Clinicians have reported that Veterans often indicate that they prefer that their names and contact information be provided directly to study staff. We'd like to make it easy for interested Veterans to get involved in research, while protecting the privacy of those Veterans who are not interested in research. Towards that end, we would like to allow a clinician to refer a participant directly to our clinic by adding the study PI or study coordinator as a co-signer to a note in CPRS in which the clinician has documented that the participant wishes to be contacted about participation.

Any Veteran who contacts or is contacted by the study team will be told that their participation is voluntary, and they may choose not to answer any questions that they find too sensitive. Also, Veterans will be told that their participation will not affect their care at the VA. The study team member will explain the study in detail, including compensation. No study procedures will begin until formal, written informed consent and HIPAA authorization have been obtained. Consent will occur by mail or via DocuSign where available. Spouses, family members, or partners who are identified by participants will provide verbal consent. We are requesting a waiver of documentation of informed consent and HIPAA for those participants.

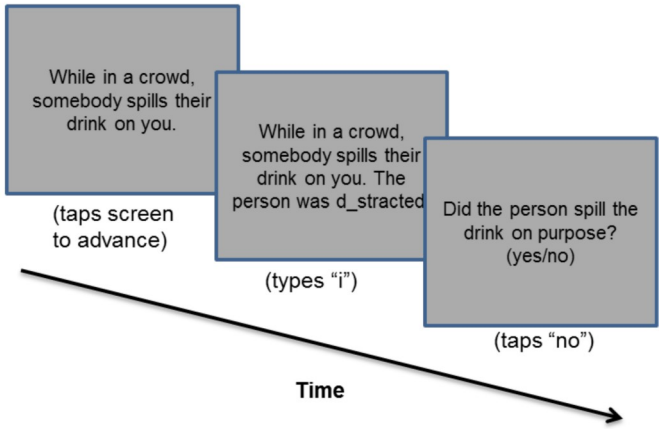
Study Interventions

In Phase/Aim 2 of the study, participants will be randomized to receive either the MIRA intervention or the Mindfulness Comparison Condition. Both interventions are described below.

MARI Intervention.

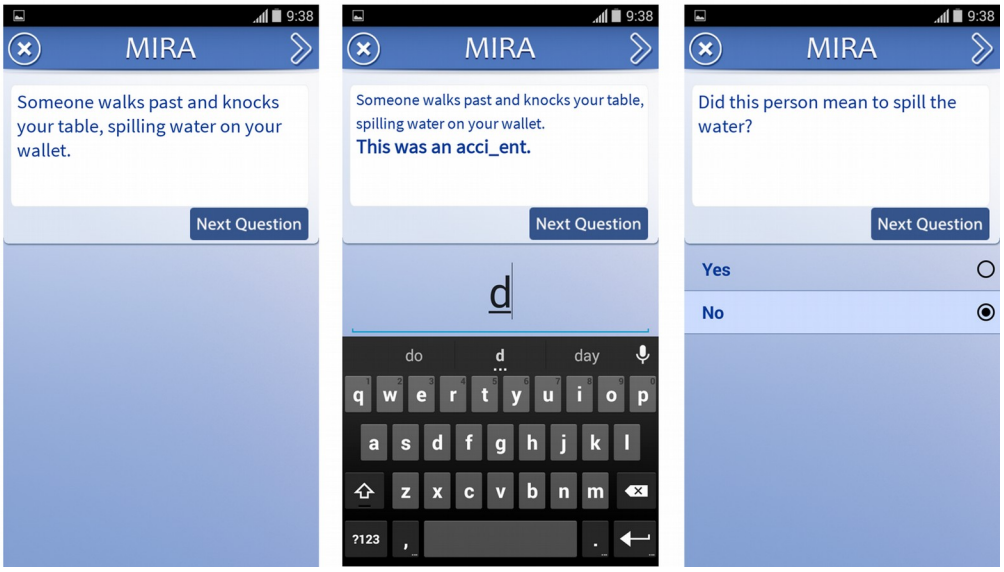
The IBM intervention. The IBM treatment works as follows (see Figure 6). Participants are shown ambiguous, anger-relevant scenarios and instructed to imagine themselves in the described situation. For example, "You speak to someone and they do not respond." Next, another sentence appears that offers a benign, non-threatening interpretation of the scenario. For example, the sentence following this particular scenario reads, "This person

Figure 6. *IBM Intervention*



is unaw_re." The participants fill in the missing letter of the word, forming the word "unaware," and assigning the benign interpretation. This interpretation is then reinforced by requiring the participants to correctly answer "yes" or "no" to a comprehension question (i.e., "Did this person hear you?"). In this example, they must answer "no" to proceed. Across treatment sessions, unique scenarios are presented (i.e., participants do not see the same scenario twice). Scenarios have been developed to capture a wide range of different themes that are likely to be anger-provoking. Themes include: physical aggression, driving situations, irritating traits of others, thinking you are being ignored by others, feeling argued with or criticized, thinking someone is stealing from you, having people block you, thinking that others have hostile feelings, feeling disrespected, thinking that people will not help you, thinking that others do not appreciate you, and thinking that situations are unfair. See Figure 7 for an example of a training scenario in the MARI app.

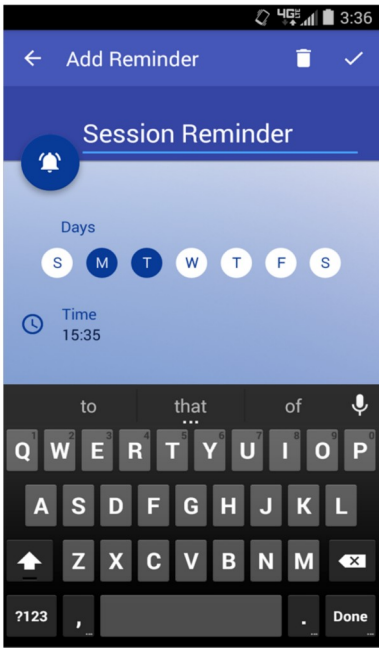
Figure 7. *Example of a Training Scenario in MIRA App*



For the purpose of this mobile application, we will be delivering the intervention daily for 4 weeks. The application will be programmed to include 28 treatments sessions that will each take approximately 10 minutes to complete. Each session will include 42 training scenarios. No scenario will be repeated across these sessions. To this end, 1,176 unique training scenarios have been developed. Quantitative and qualitative data will be collected in Aim 1(b) to determine whether this treatment schedule and dosage of treatment is feasible and acceptable and adjustments will be made based on these data. Scenarios have been reviewed by 9 PTSD experts in the field and individuals with PTSD to confirm the content is relevant to this patient population. Additionally, the reading level has been assessed using an online readability calculator ("Readability Formulas") and all scenarios are at a 6th grade reading level or less. The app will time stamp use by the participants so that treatment time and completion for each participant can be calculated.

Figure 8. *MIRA Application*

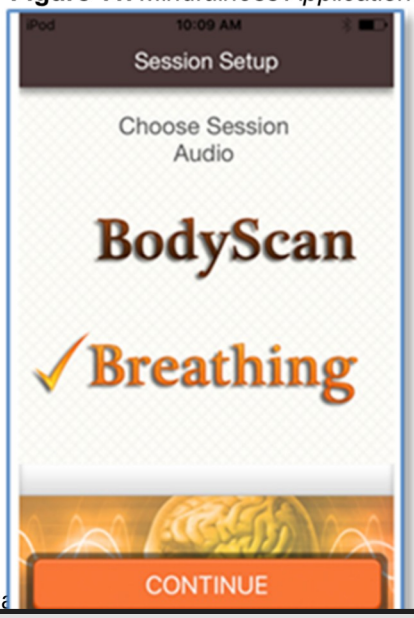
Figure 9. *Session Reminders*



Additional content. The mobile application (screenshot shown in Figure 8) will allow participants to access their treatment sessions, track their progress, and complete a daily dairy. Within the "My Progress" portion of the app, they will be able to keep track of how many sessions they have completed and see their performance across sessions in the form of a graph (e.g., number of scenarios resolved, time spent). When they start using the mobile application, they will be prompted to select which times of day would be most convenient for them to complete their treatment sessions. They will also be able to program the app to send them reminders to complete sessions, based on their selected schedule (see Figure 9). Each night, they will be prompted to complete a "Nightly Diary" entry in which they will report: 1) what their stress level was that day (0-10);2) how angry they felt that day (0-10); 3) how happy they felt that day (0-10); 4) how content they felt that day (0-10); 5) how much pain they experience that day (0-10); 6) how helpful they found the app that day (0-10); 7) whether the treatment sessions made them think or feel differently about anything that happened to them that day; and 8) if yes to question 7, they will briefly explain what happened.

Several additional tools will be programmed in order to enhance participants' engagement with the app and use of the intervention. Specifically, the application will be programmed to send participants text messages periodically. For example, when they adhere to the suggested treatment schedule (at least 5 sessions/week), they will receive a congratulatory text message at the end of that week encouraging them to keep up the frequency of sessions. Alternatively, participants who have not used the app for several days will receive a text message reminding them to do treatment sessions and offering suggestions for how to increase adherence (e.g., blocking out 10 minutes each day, setting up reminders). Participants will also be able to gain points and badges of achievement by completing treatment sessions and diary entries, as this type of reward system has been suggested to enhance motivation in mHealth interventions (Lewis et al., 2016).

Figure 11. *Mindfulness Application*



Mindfulness Comparison Condition.
Participants randomized to the comparison condition will be using an app that uses modules from the "Mindfulness Coach" app. Mindfulness Coach was created by the Department of Defense's

National Center for Telehealth and Technology in partnership with the Department of Veteran's Affairs National Center for PTSD. This app includes several exercises for practicing mindfulness skills. These exercises teach participants to increase awareness of their present thoughts, emotions, and physical sensations in a nonjudgmental and nonreactive way. Mindfulness has been found to be effective for improving psychological health among various populations (Keng, Smoski, & Robins, 2011). For the purpose of our comparison app, we have selected to include the Mindful Breathing and Body Scan exercises from the Mindfulness Coach app (see Figure 11). The Mindful Breathing exercise guides users to focus their attention on their breath, to non-judgmentally notice when they become distracted, and to then direct their attention back to their breath. The Body Scan exercise guides participants to direct their attention to different parts of their body, noticing the sensations they feel without judging or trying to change them. Each of these is 9-10 minutes (audio-guided exercises with step-by-step instructions which will allow for an equivalent time comparison for the MARI app. The design and interface of the app will be identical to the MARI application (e.g., "My Progress," "Nightly Diary," and "How to Use" components, accruing points and badges, receiving study texts). Participants will be instructed to use the mindfulness exercises for the same frequency and duration as the MARI condition.

Staff Readiness to Handle Potential Disruptive Behavior

Principal investigators in the Traumatic Stress and Health Research Laboratory have been working with Veterans with PTSD since the mid-1990s, and much of their clinical and research work has involved providing anger interventions to these Veterans. Our laboratory currently has three other studies in which we provide anger interventions to Veterans with PTSD (IRB #s 1731, 2063, and 2136). Over the course of those studies, we have not had any need to report any disruptive behaviors or contact VA police. Dillon, recently completed a quality assurance review of the proposed intervention with ten Veterans with PTSD-related anger and she is currently running a pilot study of the computer-based intervention (IRB # 2136). She has not had any Veterans express anger regarding the intervention.

Senior staff members are well trained in utilization of counseling techniques such as active listening, which helps to minimize the likelihood of angry outbursts. Study staff members are asked to attend levels 2 and 3 of the VA's Prevention and Management of Disruptive Behavior (PMDB) training, which is the VA's workplace violence prevention program. This level of training is the highest offered to VA employees in outpatient settings. Finally, office areas that are used for clinical interventions, interviews, etc. are equipped with panic alarms, and staff are trained in how/when to use the alarms.

Costs and/or Payments to Subjects

Stage/Aim 1: For the participants who participate in the first stage of the project, the study involves up to two visits. Participants who are screened and found ineligible for the study will receive $40 for their time. Eligible participants will receive $140 for completing the first visit and $100 for attending and completing the final post-treatment visit. Participants can receive up to $240 for completion of the study.

The family members/friends of the Veterans will receive $15 for each of their phone assessments, for a total of $30.

Stage/Aim2: For the participants who participate in the second stage of the project, the study involves up to three visits. Participants who are screened and found ineligible for the study will receive $40 for their time. Eligible participants will receive $150 for completing the screening/baseline visit, up to $150 for completing the pre-treatment EMA/psychophysiological monitoring, $100 for attending and completing the post-treatment visit, up to $150 for completing the post-treatment EMA/psychophysiological monitoring, and $100 for completing the 3-month follow-up visit. Participants can receive up to $650 for completion of the study.

Note that all participants will receive $50 for EMA/psychophysiological monitoring, and can receive a bonus of $50 upon their return of the equipment if they have been compliant with diary entries (i.e., have not missed more than 2 alarm-prompted entries).In order to collect the psychophysiological data on the smartphone, participants must have the study-provided, Duke-owned, phone with them at all times when they are wearing the heart rate monitor (chest strap) or the signal will disconnect. In order to increase compliance with this aspect of the study, participants will receive bonuses for the percentage of time that the have the phone in range of the HR monitor: 90+%= $50; 80-90%= $40; 70-80%= $30; 60-70%= $20; 50-60%=$10; less than 50%= $0.

The family members/friends of the Veterans will receive $15 for each of their assessments, for a total of $30.

Data and Safety Monitoring

The PI and study staff will be responsible for data safety and monitoring. There will be several ongoing mechanisms for monitoring and reporting of AEs: 1) ongoing participant contact via study personnel, 2) a toll-free number provided to participants to report concerns related to study participation; 3) weekly meetings between the PIs and study personnel. Study-related serious adverse events (SAEs) for participants in this project are not expected, but should they occur, they will be reported to the Durham VA Health Care System Institutional Review Board in accordance with local human protections program guidelines.

The PI will meet at least weekly with study personnel to discuss participants' reactions to the intervention, proper delivery of the intervention, and any adverse events or unanticipated problems. Monthly meetings between the investigators and the project manager will allow for ongoing progress reports, including the number of participants currently involved in the study, attrition rates, and scheduled data collection from participants, as well as notification and review of any AEs. Safety monitoring for AEs will be conducted in real time by the PI and/or project manager. The following information about adverse events will be collected: 1) the onset and resolution of the AE, 2) an assessment of the severity or intensity (use existing grading scales whenever possible), 3) an assessment of the relationship of the event to the study (definitely, probably, possibly or not related), and 4) action taken (e.g., none, referral to physician, start or

increase concomitant medication). The PI will determine the severity of the event, will assign attribution to the event, and will monitor the event until its resolution. Any adverse events will be reported to the IRB in accordance with the local Human Research Protection Program's Standards of Practice. All research projects conducted at the Durham VAHCS are required to have yearly IRB review. Reports of non-serious AEs are required as part of these progress reports. Additionally, any changes to the project between review periods must be application by the IRB prior to fielding.

Withdrawal of Participants
The PI may withdraw participants due to inability, or unwillingness, to complete study procedures or attend appointments.

COVID-19 Temporary Study Procedures
The informed consent process will occur over the phone or via an approved telehealth platform. Potential participants will be mailed the Duke and VA consents (along with VA HIPAA authorization), and a study staff member will call them to discuss the consents and HIPAA. Participants will be asked to return the signed consents by mail/UPS.

Study visits will be completed via an approved telehealth platform, with phone as a back-up measure. If the study staff member has access to Audacity via CAG, he/she/they will record the interviews (think-aloud and post-treatment qualitative interview) directly to the VA secured server (in lieu of videorecording with an external device). Questionnaires will be completed orally, by mail, and/or via MyHealthyVet.

Because study participants will not be able to return their equipment directly to the study staff members during their final visit, we will pay them $50 once they return the equipment to Duke and the data are transferred to VA (transfer is approved in the current protocol). We will inform participants about this payment verbally during the consent process, and again when it is time for them to return their equipment to the Duke team.

We would like to ask participants to complete measures related to stress, trauma, and coping strategies during the pandemic. New participants will complete these measures at their first visit, and ongoing participants will complete them at their next study visit. We are adding the CAIR Pandemic Impact Questionnaire (Lang, 2020; https://www.nlm.nih.gov/dr2/CAIR-PIQ_scoring.pdf), and another measure, COVID Core Questions, with variables of interest. If a participant endorses any item marked with an asterisk on the COVID Core Questions measure, we will ask them to complete a PTSD Checklist 5 related to that specific event. Because these are temporary measures to be used only during the COVID-19 pandemic, we have not added them to the consent form. Instead, participants will be informed verbally re: the measures, and will be told that they can refuse to answer them.

Safety Concerns. Study therapists will be informed that prior to beginning interviews participants will need to identify an emergency contact for the participant to be used only in true emergencies (e.g., medical crisis, high risk suicidal ideation). If any

participant expresses suicidal or homicidal ideation (SI and HI, respectively), study staff will respond using a standard of practice that has been used successfully in our lab's past telehealth-based trials. The study staff member responsible for the call will be instructed to gather more information from the participant, including information about plan, means, intent, intended victim (in the case of HI) and history of suicidal and homicidal behavior. Any participant who expressed SI will be provided with the suicide hotline number. The participant will be informed that the PI may contact him/her to talk more about his/her SI or HI. The study coordinator will obtain current contact information for the participant and inform the PI, who will contact the participant as necessary to ensure participant safety. In cases of imminent homicidality or suicidality, which are not anticipated, we will seek guidance from the Psychiatric Emergency Clinic on best strategies for follow-up, which could include, but is not limited to, self-presentation at the VA's emergency room with the help of an emergency contact, calling 911, or calling local police for a wellness check.

Data Analysis and Statistical Considerations

Stage/Aim 1: Content analysis of the qualitative interviews will be conducted according to methods described by Zhang and Wildemuth (2016). Data will be analyzed in two phases. Initially, there will be a conventional content analysis, followed by an inductive, thematic approach to identify patterns. Coded data will be analyzed for patterns and themes. Data management and coding will use ATLAS ti software (Muhr, 2004). With our total sample size across both cohorts (N =10), we estimate that we will be able to identify and address 95% of usability problems in the MIRA intervention application (Faulkner, 2003).

As well as improving app usability, data analysis and interpretation will be primarily focused on themes of: 1) session dose, timing, and frequency; and 2) treatment engagement/adherence. For example, if the majority of participants report that 5 sessions of treatment a week is too frequent or that they do not think that a 10-minute treatment session is long enough, we will adjust the treatment accordingly. We will also incorporate quantitative data (e.g., on average how many sessions participants complete) into these decisions.

We will also conduct a qualitative analysis of the weekly anger and hostile interpretation bias data by graphing these measures across time for each participant to determine if and when these measures decrease, as this will help us to determine whether there is an optimal dose of treatment and number of treatment sessions across participants.

In order to analyze descriptive data from the qualitative interviews, we will need access to NVivo 11 software, which is not available through VINCI. Therefore, deidentified data (with none of the 18 HIPAA identifiers or the study ID) will be moved to Duke University Medical Center for analysis. Only fully deidentified data will be stored on Duke computers. Any data movement to Duke will be accomplished using email. Any data transfer from Duke machine(s) back to VA will also be done via email. Data will be stored at Duke on a protected server to which only Dr. Dillon and her study staff have access; data are encrypted at rest.

Stage/Aim2: Recognizing that it is inappropriate to examine efficacy in a small pilot trial, we will focus on feasibility and acceptability objectives (Leon et al., 2011). As appropriate for this stage of treatment development and evaluation, analysis and interpretation will focus on describing the primary outcomes: acceptability of the intervention and feasibility of the trial approach. We will examine the recruitment rate, treatment retention, patient satisfaction, and app utilization as primary outcomes.

We will also describe Nightly Diary outcomes, including: daily emotions and pain reported; how helpful the app was; whether it made them feel differently about things that happened during their day. Additionally, although we will not be able to statistically analyze group differences, we will describe group differences in clinical (anger-related) outcomes and functional outcomes, including whether changes were observed in the expected directions (reductions in anger variables and increases in functional outcomes).

Finally, mixed between-within repeated measures ANOVA will be used to examine potential treatment effects on overall HRV. Specifically, 2 (Treatment) X 2 (Time) ANOVAs will be used to model SDNN, LF, and HF to determine whether overall HRV increases from pre- to post-treatment as a result of IBM relative to the control condition. We will also examine changes from pre- to post-treatment in physiological reactivity to anger. Using methodology that we have applied to examine mood-related autonomic arousal (e.g., Dennis et al., 2017), we will use multilevel modeling (MLM) to examine short-term changes in HRV and HR associated with momentary assessments of anger. MLM is appropriate for analyzing unbalanced repeated-measures data and can incorporate both person-level predictors (e.g., treatment condition) and episodic predictors (e.g., anger; . We will thus examine whether the association between anger and autonomic arousal (i.e., HR, SDNN, LF, and HF) attenuates following treatment, particularly for participants assigned to the MIRA condition. We will also examine whether this expected decrease in autonomic reactivity is associated with improved functional outcomes and decreased anger outcomes.

Privacy, Confidentiality, and Information Security

1. Lists of Data Reviewed and/or Collected for Screening/Recruitment and Conduction of Study:

The Personal Health Information that will be obtained, used, and/or shared for this study includes:

Identifier(s)	Source(s) of Health Information
☒ Names	☐ Medical history & physical exam information
☒ All geographic subdivisions smaller than a State, including street address, city, county, precinct, and zip code. Describe: Participants' addresses will be collected during the study in order to pay them for participation.	☒ Photographs, videotapes, audiotapes, or digital or other images

Identifier(s)	Source(s) of Health Information
☒ All elements of dates (except year) for dates directly related to an individual, including birth date, admission date, discharge date, visit or treatment dates, etc.; and all ages over 89, Describe: Date of participation will be collected. In addition, treatment records, laboratory results, etc. will be collected.	☐ Biologic specimens (e.g., blood, tissue, urine, saliva). Describe:
☒ Telephone numbers	☒ Progress notes
☐ Fax numbers	☒ Diagnostic / Laboratory test results
☒ Electronic mail addresses	☐ Operative reports
☒ Social Security Numbers	☐ Imaging (x-ray, CT, MRI, etc.)
☒ Medical record numbers	☐ Discharge summaries
☐ Health plan beneficiary numbers	☒ Survey / Questionnaire responses
☒ Account numbers	☒ Billing records
☐ Certificate and/or license numbers	☐ HIV testing or infection records
☐ Vehicle identifiers and serial numbers, including license plate numbers	☐ Sickle cell anemia information
☐ Device identifiers and serial numbers	☒ Alcoholism or alcohol use information
☐ Web Universal Resource Locators (URLs)	☒ Drug abuse information
☐ Internet Protocol (IP) address numbers	☒ Mental health (not psychotherapy) notes
☐ Biometric identifiers, including finger & voice prints	☐ Psychological test results
☐ Full-face photographic images and any comparable images	☐ Genetic testing
☒ Any other unique identifying number, linked study ID, characteristic, or code, describe: study ID number	☐ Other, describe:

2. Data and/or Specimen Acquisition:

Data for this study will be collected through (*check all that apply*):

☒ Prospective data and/or specimen collection obtained from participants. Provide description of processes: Data will be obtained through self-report questionnaires, semi-structured interviews, and app utilization.

☒ Retrospective data collection and/or specimens obtained from medical chart review/ data access. Describe how data will be obtained (e.g., fileman, CDW, etc.): In accordance with a Waiver or Alteration of HIPAA Authorization, names, addresses, telephone numbers, social security numbers, and diagnostic information of potential participants will be obtained from the VA's Regional Data Warehouse.

☐ Retrospective data collection and/or specimens obtained from an IRB-approved data and/or specimen repository. Indicate the repository source including name, VA location, and IRB number: .

Note: for data and/or specimens obtained from a VA approved data repository, a Data Use Agreement (DUA) must be executed prior to obtaining data and/or specimens. See VHA Handbook 1200.12 for further information.

3. Level of Data:

The following level(s) of data will be acquired/maintained for this study (*check all that apply*):

☒ Identified (e.g., names, addresses or other identifiers included)
☒ Coded (direct and/or all identifiers removed, but study code/ID included)
☒ De-Identified (all HIPAA 18 and study ID/code removed):
- ☐ Verified Statistically
  OR
- ☒ Verified by Absence or Removal of HIPAA 18 and study ID

☐ Limited Data Set
☐ Other: Describe:

4. Location of Data and/or Specimens, and Data Retention Plan:

A. Data and/or Specimen Location: Data will be stored electronically in \\ VHADURFPC02B\groups1\Nicotine Research\Study Information\Study Logbooks\ Kirsten CDA and \\VHADURFPC02B\groups1\Nicotine Research\Study Information\ Study Databases\Kirsten CDA. Data that will be stored electronically include name, address, phone number, social security number, amount of study payment earned, and date of visits (in Study Logbooks location). The study logbook will contain the key connecting PHI and the study identification number. Paper records of data include study consent form and HIPAA authorization (identified), questionnaire responses, and interview notes (coded). Audio recordings of interviews will be captured using an Olympus VN-722PC. When not in use, the audio recorder will be stored in a locked file cabinet in our study offices at building 1, Durham VA Medical Center. Recordings will be moved from the audio recorder to the "Study Logbooks" location listed above; our laboratory has sanctuary exemption to allow these devices to plug into the network, as they are used in other current research projects. For long term storage, audio recordings may be moved to an encrypted DVD that is password-protected. Any encrypted DVDs will be stored in a locked filing cabinet in a locked office. Transcriptions from the study interviews will be stored electronically at the Study Logbooks location listed above. Study data collected via a Duke IRB protocol will be combined with VA data. Data will be transferred via a VA-owned FIPS-encrypted thumbdrive or via VA's S.A.F.E.

☒ Data will be also be placed at the VA Informatics and Computing Interface (VINCI; http://vaww.vinci.med.va.gov/vincicentral/VINCIWorkspace.aspx). The VA Informatics and Computing Infrastructure is a partnership between the VA Office of Information Technology and the Veterans' Health Administration Office of Research and Development. Researchers and operations staff can use VINCI to access data and statistical analysis tools in a virtual working environment through a certified VHA network computer using the VA Intranet or Virtual Private Network (VPN).

B. Data Retention Plan

☒ Research records will be maintained and destroyed according to the National Archives and Records Administration, Records Schedule Number: DAA-0015-2015-0004. Records destruction, when authorized, will be accomplished using the then current requirements for the secure disposal of paper and electronic records. Currently, destruction of research records (see DAA-0015-2015-0004, section 7.6 "Research Investigator Files" for materials included in research records) is scheduled for 6 years after the cut-off (the cut-off is the completion of the research project) and may be retained longer if required by other federal agencies. Records will not be destroyed without pre-notification to the facility records manager.
☐ Other data retention plan, describe:

5. Data Access and Data Recipients: Only members of our DVAMC research team will have access to identifiers and coded data. In order for data analysis to occur using NVivo 8, ATLAS.ti, and SAS software, a de-identified dataset will be uploaded to VINCI for analysis using VA-owned data analysis software (NVivo 8).

In order to analyze descriptive data from the qualitative interviews, we will need access to NVivo 11 software, which is not available through VINCI. Therefore, deidentified data (with none of the 18 HIPAA identifiers or the study ID) will be moved to Duke University Medical Center for analysis. Any data movement to Duke will be accomplished using email. Any data transfer from Duke machine(s) back to VA will also be done via email. Data will be stored at Duke on a protected server to which only Dr. Dillon and her study staff have access; data are encrypted at rest.

All VA research personnel who have access to VHA records are instructed, in accordance with VA policy, on the requirements of Federal privacy and information laws and regulations, VA regulations and policies, and VHA policy. All study personnel who are VA employees working within the VA system have fulfilled all required HIPAA and other VA security and privacy policy training requirements and have agreed to follow guidelines pertaining to the protection of patient data. All research staff sign VA Rules of Behavior, and all study staff are up-to-date with VHA Privacy Policy Training and the VA Office of Cyber and Information Security Awareness Training Course. The data security and privacy procedures summarized in that course include logging off or locking the computer when walking away from it; no sharing of access codes, verify codes or passwords; not allowing anyone else to use the computer under one's password; and disposing of sensitive information using VA-approved methods (e.g., shredder bins). Access to study data will be removed for all study personnel when they are no longer part of the research team.

Study visits will either be conducted at the main VA Hospital or at the MIRECC at Croasdaile, based on participant preference and space availability. Data that is transported between the main hospital and Croasdaile offices will be secured in a lockable briefcase.

6. Data and/or Specimen Transportation and/or Transmission for all data and/or specimens involved in the study:

I. ☐ Data and/or specimens will not be transported or transmitted outside of Durham VAMC environment.

II. ☒ Data and/or specimens will be transported BETWEEN sites that are under the auspices of the Durham VA Medical Center.

III. ☐ Data and/or specimens will be transmitted to other VA sites using the following method(s):

A. Data

☐ Data are de-identified and thus will be sent via unencrypted e-mail or unencrypted disk (encryption is optional).

☐ Data are coded or contain identifiers and thus will be sent

☐ Other, describe:

B. Specimens

☐ Specimens are de-identified and thus will be sent via standard carrier (tracking is optional).

☐ Specimens are coded or contain identifiers and thus will be sent via VA-authorized carrier with tracking.

☐ Other, describe:

IV. ☒ Data and/or specimens will be transported to non-VA/VHA sites (e.g., academic affiliates, laboratories, etc.) using the following method(s):

A. Data

☒ Data are de-identified and thus will be sent via unencrypted e-mail or unencrypted CD.

☐ Data are coded or contain identifiers and thus will be sent via <chose method of transfer such as FIPS 140-2 encrypted CD or FIPS 140-2 encrypted hard drive/flash drive> using VA—approved carrier with tracking.

☐ Data are coded or identified and will be uploaded to sponsor website using electronic case report form (eCRF) <insert information including sponsor name and URL and the encryption the site uses.>

☐ Other, describe:

B. Specimens

☐ Specimens are de-identified and thus will be sent via standard carrier (tracking is optional) or will be hand-delivered by research study personnel. Specify method of delivery:

☐ Specimens are coded and thus will be sent via VA-approved carrier with tracking or will be hand-delivered by research study personnel. Specify method of delivery:

In accordance with the HIPAA and the Privacy Act, for any coded or identifiable data or specimens released from the Durham VAMC (with the exception of Limited Data Sets), an Accounting of Disclosure (AOD) will be maintained (e.g., in a database or spreadsheet) that includes the participant's name, date of the disclosure, description of the nature of the Individually Identifiable Information (III) disclosed, purpose of each disclosure, and the name and address of the person/agency to whom the disclosure was made.

C. ☐ Local DVAMC memorandum "Authorization to Use, Process, Store, or Transmit VA Sensitive Information Outside VA Owned or Managed Facilities" has

been pre-filled out for each study team member who may transport the data and/ or specimens off-site. This (these) forms are included with the IRB materials.

D. ☐ Containers (e.g., briefcase, bin) are labeled with the following notice (label placed on the outside of container) in accordance with VHA Directive 6609:

NOTICE!!!
Access to these records is limited to: AUTHORIZED PERSONS ONLY. Information may not be disclosed from this file unless permitted by all applicable legal authorities, which may include the Privacy Act; 38 U.S.C. §§ 5701, 5705, 7332; the Health Insurance Portability and Accountability Act; and regulations implementing those provisions, at 38 C.F.R. §§ 1.460 – 1.599 and 45 C.F.R. Parts 160 and 164. Anyone who discloses information in violation of the above provisions may subject to civil and criminal penalties.

7. Risk Mitigation Strategies:

☒ Data are fully de-identified (stripped of HIPAA 18 and study ID/code) before being shared outside of Durham VAMC.

☐ Specimens are fully de-identified (stripped of HIPAA 18 and study ID/code before being shared outside of Durham VAMC.

☒ Direct identifiers will be maintained separately from data and or specimens by using a code to "identify" subjects. In a separate database (i.e., a "linking" or "cross-walk" database) this code will be linked to identifying subject information.

☐ Other, specify:

8. Suspected Loss of VA Information:

Should any incident such as theft or loss of data, unauthorized access of sensitive data or non-compliance with security controls occur it will be immediately reported according to VA policy. All incidents regarding information security/privacy incidents will be reported to the ISO and PO within 1 hour of acknowledgement of issue and done so using the VHADUR Research Events Report e-mail group (VHADURResearchEventReport@va.gov).

9. Reporting of Results:

☒ Reporting of results, such as in scientific papers and presentations, will never identify individual subjects. Data will be presented in aggregate and individual-level data will not be published.

☐ Other results reporting plan, describe:

10. Future Use of Data:

☐ Data will be retained for future use. This is described elsewhere in the protocol and is noted in the HIPAA authorization.

- ☐ Future Use of data is optional (i.e., not required by the research subject).
- ☐ Future Use of data is required for participation in the study.

☒ No future use of data is currently planned.

11. Use of Mail Merge Technology

☒ Mail merge programs will be used to generate letters and/or address labels for mailings to potential or already enrolled research subjects. The study team is aware that to reduce risk of mail merge related privacy incidents, use of mail merge programs requires a 25% accuracy check to verify that (potential) research subject name and mailing address are properly "matched". If discrepancies are found, a 100% accuracy check is required before letters may be mailed.

12. Use of Non-Standard Software
☒ I do NOT intend to use any new specialized software (i.e. Software that's not already approved OR installed) in this study.

☐ I intend to use specialized software that has not already been installed and it has been approved for use by the VA Technical Reference Model (TRM) Group.
(Note: All new software must be approved by TRM before it can be installed on VA systems.)

☐ I intend to use previously installed software on my VA computer.

13. Use of Cloud Computing Services
☒ Cloud computing services will NOT be used in this study.

☐ Cloud computing services WILL be used in this study as described below and have been approved nationally by the VA Chief Information Officer (CIO). (Note: ONLY cloud computing services that have been approved nationally may be used.)

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