

Study Title: An RCT of CBT Telephone for Late-Life GAD

Principal Investigator: Gretchen A. Brenes, Ph.D.

Co-investigators: Elizabeth Arnold, Ph.D.
Suzanne Danhauer, Ph.D.
Mary Lyles, M.D.
W. Vaughn McCall, M.D.
Michael E. Miller, Ph.D.

Sponsor/funding source: NIMH

Background, Rationale, and Context

Anxiety disorders are the most prevalent psychiatric disorders (Kessler et al., 2005). Among older adults, anxiety is more common than depression (Regier et al., 1988; Kessler et al., 2005); yet research on the nature and treatment of anxiety has lagged far behind that of depression (Wetherell, Lenze, & Stanley, 2005). Generalized Anxiety Disorder (GAD) is characterized by excessive, uncontrollable worry and somatic symptoms, and is the second most prevalent anxiety disorder in older adults (Krasucki, Howard, & Mann, 1999). Prevalence rates of GAD in community-dwelling older adults range up to 7.3% (Beekman et al., 1998). The effects of GAD extend beyond mental health. GAD is associated with significant economic burden (Andlin-Sobocki & Wittchen, 2005), poorer quality of life (Stanley, Hopko, Diefenbach et al., 2003; Wetherell, Gatz & Caske, 2003), increased comorbidity (Krasucki, Howard, & Mann, 1999), sleep disturbances (Stanley, Hopko, Diefenbach et al., 2003), and increased service use (Stanley et al., 2001).

Cognitive behavioral therapy (CBT) is the most efficacious nonpharmacological treatment for GAD (Borkovec & Ruscio, 2001) and is the only nonpharmacological treatment systematically evaluated with older GAD patients (Ayers, Sorrell, Thorp, & Wetherell, 2007). The efficacy of CBT for the treatment of late-life GAD has been established in 6 randomized controlled trials (Mohlman et al., 2003; Mohlman & Gorman, 2005; Stanley, Beck, & Glassco, 1996; Stanley, Beck, Novy et al., 2003; Stanley, Hopko, Diefenbach et al., 2003; Wetherell et al., 2003). However, limitations of these studies may reduce the generalizability of their findings. Most importantly, attrition rates were high (up to 33%) which may reflect dissatisfaction or difficulty overcoming barriers. Additionally, 5 out of 6 studies were conducted in academic settings and the treatments required up to 15 face-to-face sessions. Furthermore, half of the studies provided treatment in a group format, producing even more constraints. Anxious older adults face many barriers to treatment that were not addressed in these studies. Therefore, it is not known if previous findings will generalize to community-dwelling older adults. Studies are needed that apply to community-dwelling elders, both by reducing their barriers to treatment and increasing their access to treatment.

Conducting treatment using telephone therapy and written materials reduces barriers that older adults face. This includes the stigma associated with mental health treatment, as treatment can be conducted within the privacy of one's home. No face-to-face visits are required, eliminating any transportation barriers. Bibliotherapy with telephone therapy also increases the accessibility to mental health services for the many people who live in underserved areas and lack access to a trained geriatric cognitive-behavioral therapist. This format is particularly

appropriate for older adults because there are fewer time constraints. In a typical CBT intervention, patients attend 8 to 16 weekly 50-minute psychotherapy sessions. Participants are taught CBT principles and techniques and are instructed on how to apply them to their daily lives. Therefore, sessions must be very structured to complete the treatment. However, older adults need more time to process information in psychotherapy, especially since those with GAD have impairments in short-term memory (Mantella et al., 2007). Thus, an intervention that provides more ways and more time to process information may be particularly beneficial for older adults. The combination of telephone therapy and written materials allows older adults to process information both visually and verbally. The written format provides older adults with an easy opportunity to read and review the materials as often as needed and at their own pace. In our current study, older adults report that they frequently reread and highlight information (Brenes, McCall, Williamson, & Stanley, in press). By presenting written information beforehand, the telephone session can be used to briefly review materials and answer questions, but mostly cover the application of anxiety management techniques in the participant's daily life.

Objectives

Primary Aim: To examine the efficacy of cognitive-behavioral therapy-telephone (CBT-T) for reducing anxiety and worry in older adults with GAD.

Hypothesis 1: Participants who receive CBT-T will demonstrate a greater reduction in anxiety symptoms as assessed by the Hamilton Anxiety Rating Scale than participants who receive nondirective supportive therapy-telephone (NST-T).

Hypothesis 2: Participants who receive CBT-T will demonstrate a greater reduction in worry symptoms as assessed by the Penn State Worry Questionnaire-Abbreviated than participants who receive NST-T.

Secondary Aim: To examine the effects of CBT-T for improving coexistent symptoms (depressive symptoms, sleep) and functional status (disability, quality of life) in older adults with GAD.

Hypothesis 3: Participants who receive CBT-T will demonstrate a greater improvement in depressive symptoms as assessed by the Beck Depression Inventory-Second Edition and sleep as assessed by the Insomnia Severity Index than participants who receive NST-T.

Hypothesis 4: Participants who receive CBT-T will demonstrate a greater improvement in disability as assessed by the Pepper Center Tool for Disability and quality of life as assessed by the SF-36 than participants who receive NST-T.

Exploratory Aim: To examine potential moderators (age, education, gender, race, income, medical comorbidity, baseline anxiety severity, baseline psychotropic medication use, baseline comorbid depressive disorders, and therapist assignment) and mediators (new psychotropic medication use, therapeutic alliance, adherence, patient satisfaction, and treatment credibility) of treatment on anxiety and worry.

Design

We have proposed a randomized controlled trial comparing 1) cognitive behavioral therapy delivered by telephone (CBT-T) with 2) nondirective supportive therapy (NST-T) for the treatment of late-life GAD in a sample of underserved older adults. Eight-eight participants will be randomized into each of the two conditions. Participants will be recruited from the 41

counties in North Carolina with an urban population of < 20,000 people. CBT-T consists of up to 10 workbook chapters accompanied by 8 to 12 weekly 45-50 minute psychotherapeutic telephone calls. When participants in the CBT-T condition complete the workbook, they will then receive an additional 4 telephone booster sessions over the next 3 months. Participants in the NST-T condition will receive weekly 45-50 minute nondirective supportive therapy telephone calls for 10 weeks. In the event that a participant becomes unable to complete weekly sessions due to a health problem (e.g. heart attack, surgery), we will allow for a recovery period and place the weekly sessions on hold until the participant can resume participation in the study. Assessments will be conducted by telephone pre-randomization and at approximately 2 months post-randomization, 4 months post-randomization, 9 months post-randomization, and 15 months post-randomization. **Primary outcomes** include a clinician-rated anxiety measure and a self-report measure of worry. **Secondary outcomes** include depressive symptoms, physical disability, quality of life, sleep, and GAD severity. Exploratory analyses will examine potential moderators and mediators of treatment outcomes. We hypothesize that CBT-T will produce significantly greater improvements in anxiety, worry, physical disability, depressive symptoms, sleep, and quality of life than NST-T.

Inclusion and exclusion criteria

Inclusion criteria include: 1) age \geq 60 years, 2) a principal or co-principal DSM-IV diagnosis of GAD as assessed by the SCID-IV, 3) residency in a county with an urban population of < 20,000 people, and 4) proficiency in English. Principal diagnosis is defined as the disorder with the highest global severity rating. When 2 diagnoses meet this criterion, co-principal diagnoses will be assigned.

Exclusion criteria include: 1) current psychotherapy; 2) a DSM-IV diagnosis of active alcohol or substance abuse with substance use within the last month; 3) a diagnosis of dementia or global cognitive impairment based on the education-adjusted scores on the Telephone Interview for Cognitive Status-modified (TICS-m); 4) psychotic symptoms; 5) active suicidal ideation with plan and intent; 6) any change in psychotropic medications within the last 1 month and 7) any hearing loss that would prevent a person from participating in telephone sessions.

Sample Size

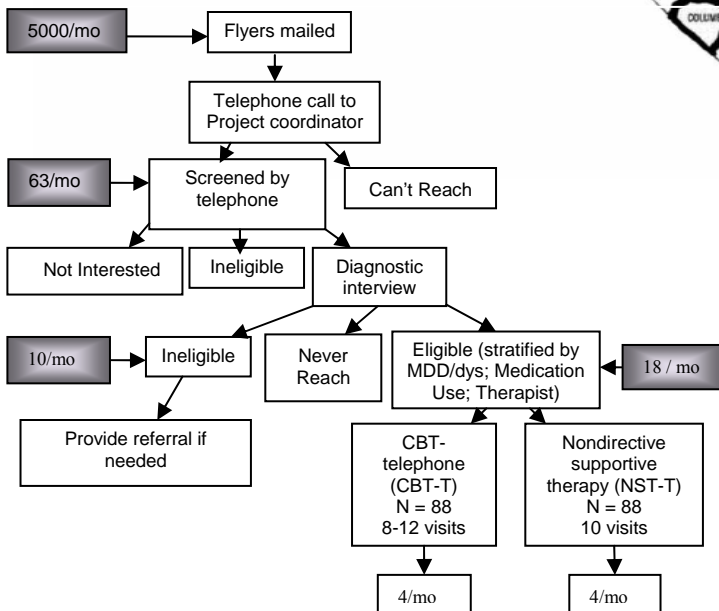
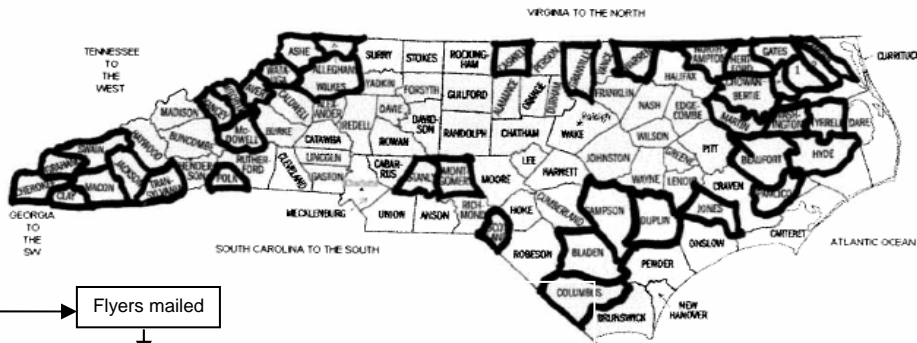
We used data from a pilot study (N = 55; N = 29 in usual care with referral and N = 26 in CBT-T) and determined the sample size for this randomized trial comparing CBT-T with NST-T for reducing anxiety and worry in older adults with GAD. Analyses of data from this pilot provided estimates of the standard deviation (SD) for the Penn State Worry Questionnaire-A (PSWQ-A) and Hamilton Anxiety Rating Scale (HAM-A) scores: these values were 6.7 and 7.2, respectively. The correlation between baseline and post-intervention PSWQ-A scores was 0.45 and the correlation between baseline and post-intervention HAM-A scores was 0.50. We consider a $\frac{1}{2}$ SD difference on the PSWQ-A and the HAM-A in the post-intervention means as the minimally important detectable difference. This intervention difference corresponds to approximately a 3.35 difference in post-intervention means for both the PSWQ-A and the HAM-A. A repeated measures analysis of covariance will be used with a contrast to test the hypothesis of no intervention effect at the post-randomization visit. Using the pilot data estimates of SD (6.7 for the PSWQ-A and 7.2 for the HAM-A) and correlation (.45 for the PSWQ-A and .50 for the HAM-A) between baseline and follow-up outcomes provided above, power calculations for analysis of covariance on the PSWQ-A outcome indicate the need for a total of 80

participants per group to attain 90% power. We have inflated the **sample size to 88** observations per group to account for an expected drop-out rate of approximately 10%. Our evaluable sample size of 80 per group will provide approximately 90% power to detect differences in follow-up means of 2.9 for the BDI-II, 10.8 for the SF-36, 5.1 for the Pepper Center Tool for Disability, and 2.3 for the Insomnia Severity Index. These mean differences correspond to effect sizes of 37%, 40%, 48%, and 40% for these four measures, respectively.

Recruitment procedure

We will employ multiple recruitment strategies. 1.) We will mail a flyer describing the study to all older adults residing in the targeted recruitment counties using a commercial mailing list. The flyer will be written in lay terms at an 8th grade reading level. All individuals 60 years and older in the 41 NC counties with populations of <20,000 people will be targeted to receive a brochure. 2.) We will mail a letter to local physicians, churches, and community agencies to describe the study and request that they distribute enclosed recruitment flyers to interested individuals. 3.) We will mail a letter to all randomized participants encouraging them to tell their family and friends about the study. 4.) We will recruit participants through senior centers and senior programs, senior housing centers, health fairs, and health clinics. The counties to be targeted are outlined in Figure 1.

Figure 1. Rural and small urban counties in NC



Screening

The recruitment flyer will instruct interested persons to call our toll-free telephone number. Using a script, the project manager will describe the study and screen these persons by telephone. The screening will consist of the PSWQ-A and the TICS-m. Questions will also assess current psychotherapy use; current alcohol or drug problems within the last month;

diagnosis of dementia; and psychotropic medication use and changes in dosage within the last month. Participants recruited at senior centers and senior programs, senior housing centers, health fairs, and health clinics will have the option of being screened onsite in a private location or they can choose to be screened by telephone. Participants who score ≥ 16 on the PSWQ - A and meet the other inclusion/exclusion criteria will be scheduled to complete a SCID interview. Participants will also be asked to provide the names and phone numbers of 2 people as emergency contacts. Eligible participants will be randomly assigned to either CBT-T or NST-T, and will be randomized to 1 of 2 therapists who will provide all of the treatment.

Study assessments

A combination of interviewer-based and self-report measures will be administered pre-randomization and at approximately 4 months post-randomization, 9 months post-randomization, and 15 months post-randomization. At approximately 2 months post-randomization, participants will also complete an abbreviated battery consisting of the primary outcomes and depression measure. Rates of recruitment are slower than originally estimated. As a result, funding may end before the 9 month and 15 month assessments can be completed. Therefore, we propose the following: Participants who are randomized before August 1, 2013 will receive all follow up assessments. Participants randomized between August 1, 2013 and February 28, 2014 will receive only the 2, 4, and 9 month assessments. Participants randomized between March 1, 2014 and June 30, 2014 will receive only the 2 and 4 month assessments. We will attempt to complete all follow-up assessments if there are any carry over funds left at the end of the grant (December 31, 2014). All interviewer-based measures will be administered by telephone by a trained assessor who will be blinded to treatment condition. Self-report measures will be mailed to the participants with a stamped return envelope enclosed. If any assessment indicates the need for immediate treatment (e.g., active psychosis, active suicidal intent), the PI and the project manager will be notified and the crisis protocol will be followed. We estimate that participants will complete the telephone diagnostic interview in approximately 90 minutes and the self-report measures in approximately 30 minutes. In addition to the free care that participants will receive, they will be compensated \$25 for completing each of the 3 assessment batteries (diagnostic interview and self-report measures). **Primary outcomes** include clinician-rated anxiety (HAM-A) and self-report worry (PSWQ-A). **Secondary outcomes** include depressive symptoms (BDI-II), disability (PCT-D), quality of life (SF-36), sleep (ISI), severity of GAD, and self-reported DSM-IV symptoms of GAD (GAD-7). **Moderators** include age, education, gender, race, income, medical comorbidity, baseline GAD severity, baseline use of psychotropic medication, baseline current depressive disorder, type of rural county (adjacent to metro area vs. not adjacent to metro area), success of blinding, and therapist assignment. Mediators include services utilization, new psychotropic medication use, therapeutic alliance, adherence, patient satisfaction, and treatment credibility (see Table 1).

Table 1. Timetable of measurements.

	Screening	Pre-randomization	Approximately 2 mo. Post-randomization	Approximately 4 mo. Post-randomization	Approximately 9 mo. Post-randomization	Approximately 15 mo. Post-randomization
Diagnostic measures						
Telephone screening measure (T)	X					
SCID-IV (T)	X			X	X	X
Telephone Interview for Cognitive Status-modified (T)	X					
Anxiety measures						
Penn State Worry Questionnaire-Abbreviated	X	X	X	X	X	X
Hamilton Anxiety Rating Scale (T)		X	X	X	X	X
Other outcome measures						
Beck Depression Inventory-Second Edition		X	X	X	X	X
Pepper Center Tool for Disability		X		X	X	X
SF-36		X		X	X	X
Insomnia Sleep Index		X		X	X	X
GAD-7		X		X	X	X
Demographic and health-related information						
Demographics		X				
Cornell Services Index (T)		X		X	X	X
Health		X				
Medication Use (T)		X		X	X	X
Process measures						
Adherence	OCCURS AFTER EACH THERAPY SESSION					
Expectancy Rating Scale		X		X		
Client Satisfaction Inventory				X		
Working Alliance Inventory				X		
Success of Blinding				X		
Other measures						
Barriers to Psychotherapy		X				
Use of Other Services				X	X	X

Note: T indicates the measure is administered by telephone. All other questionnaires are paper and will be included in the mailed packet and completed by the participants.

Assessors and training

All interviewer-administered measures, including the SCID, HAM-A, and Cornell Services Index, will be administered by a primary assessor and audio taped. Assessors will be trained to reliability and diagnoses will be verified by a weekly diagnostic consensus conference in order to

reduce rater drift. In addition, 20% of interviews will be reviewed by a second assessor who will be blind to the diagnoses and ratings made by the primary assessor. Inter-rater reliabilities (kappa) and intraclass correlation coefficients (ICCs) will be computed for DSM-IV diagnoses, severity of GAD ratings, and HAM-A ratings. In order to minimize any potential bias, the assessors will have no connection with the study therapists and will not have access to participant files. After randomization, participants will be instructed not to divulge any information about their treatment to the assessor. When scheduling assessments, the project manager will ask participants not to reveal their group assignment to the assessor. Furthermore, at the start of the post-intervention and follow-up interviews, the assessor will inform the participant that he/she is blind to treatment condition and ask the participant not to mention any information that would unblind the assessor. Upon completion of the post-treatment assessment, assessors will be asked to indicate if the participant unblinded them, indicate which condition they think a participant is in, and rate their degree of certainty of group assignment. We will also examine the relationship between success of blinding with outcomes.

Cognitive behavioral therapy-telephone (CBT-T)

Telephone therapy. Weekly telephone sessions with the randomly assigned therapist will last 45 to 50 minutes. In order to ensure privacy, every participant will be asked if he/she needs to reschedule the appointment due to a lack of privacy. All sessions will start with a review of homework and any problems or stressors they have encountered within the context of the homework. The therapist and the participant will discuss if anxiety coping skills were used and were effective. If so, use of the coping techniques will be reinforced. If the anxiety was not adequately managed, coping skills will be reviewed and ways to incorporate or improve their use will be identified. The study therapist will then review the assigned chapter and the exercise with the participant. The participant will be encouraged to ask questions about the reading materials and discuss any in implementing the anxiety technique. If a participant reports difficulty with a particular chapter or technique, he/she will be instructed to continue to work on that chapter and technique for another week and another call will be scheduled. The study therapist will only send the next chapter when confident that the participant fully understands the current chapter. Upon completion of the workbook, booster sessions will be used to reinforce anxiety management skills and problem-solve. Booster sessions will be provided at 2 weeks, 4 weeks, 8 weeks, and 16 weeks after completion of the treatment.

Workbook. The PI adapted the 10-chapter workbook from the Controlling Anxiety in Later-Life Medical Patients workbook developed by Wetherell and colleagues (Wetherell, Sorrell, Thorp, & Patterson, 2005). The techniques in this CBT intervention have demonstrated efficacy in treating adults with GAD (Borkovec & Whisman, 1996; Gould, Otto, Pollack, & Yap, 1997) and older adults with GAD (Stanley, Beck, & Glassco, 1996; Stanley, Beck et al., 2003; Wetherell et al., 2003). Chapter 1 describes the treatment and presents a cognitive behavioral model of anxiety. Chapters 2 through 9 each address a specific anxiety management technique or a specific problem that may be comorbid with anxiety. Chapters are approximately 5 to 10 pages long and are written in lay terms. They are presented in a large font and key points are highlighted and reiterated simply to aid readers in fully understanding the content. Each chapter contains multiple examples of specific situations that an older adult might experience. Chapters are also focused on techniques that are more relevant to older adults, such as sleep and pain, rather than assertiveness skills and time management. The sleep and pain chapters are optional. There are 3 ways to trigger the use of the pain and sleep modules: 1) the participant mentions

problems with pain or sleep during the course of the telephone sessions with the therapist; 2) the participant requests the pain and/or sleep modules; 3) the participant scores below the mean ($M = 67.5$) for older adults on the pain scale from the SF-36 as lower scores indicate greater pain (Ware, Kosinski, & Gandek, 2003) or > 7 on the Insomnia Severity Index indicating at least subthreshold insomnia (Bastien et al., 2001); if the participant meets any of these criteria, an automatic notification will be sent to the project manager who will alert the therapist to provide these chapters. Each chapter is followed by a homework exercise to practice the technique described in that chapter. A completed example is provided followed by blank copies to be completed by the participant. The homework is used to encourage the application of the techniques to the reader's daily life. All chapters will also be available on audiotape for participants who have difficulty reading. It is expected that participants will complete 1 chapter per week. Participants are allowed to complete the workbook within 8 to 12 weeks of randomization. The minimum amount of time to complete the 8 mandatory chapters is 8 weeks. The additional 4 weeks provides time for participants to complete up to 2 optional chapters (pain and sleep) and/or spend 2 weeks on up to 4 chapters that they may find difficult.

Nondirective supportive therapy-telephone (NST-T)

Nondirective supportive therapy will follow Borkovec's protocol (Borkovec & Costello, 1993; Borkovec, Newman, Pincus, & Lytle, 2002). NST-T provides a "high-quality therapeutic relationship that provides a warm, genuine, and accepting atmosphere through the use of supportive and reflective communications" (p. 9); it does not provide advice, suggestions, or coping methods. Borkovec reports high levels of treatment credibility and therapeutic relationship (Borkovec & Costello, 1993). NST-T will be conducted by telephone via weekly 45-50 minute sessions with the randomly assigned therapist. Participants in the NST-T condition will receive 10 sessions. This number was chosen because it is the average number of sessions a participant in the CBT-T condition can receive (minimum of 8 sessions and maximum of 12 sessions). The NST-T condition matches the CBT-T condition in terms of amount of therapist contact (equivalent session length, number of sessions, and frequency of sessions) and delivery of treatment (via telephone).

Therapist training protocol and supervision

There will be 2 therapists for this study, each of whom will deliver both treatments. Training for each of the treatments will include use of the treatment manual, formal didactic presentations, readings, role plays, and 2 closely supervised training cases. Further, there will be 2 independent experts (Drs. Arnold and Stanley) rating therapist adherence and competence in each of the interventions. The competency of therapists in delivering CBT-T will be evaluated with a measure developed and used by Dr. Melinda Stanley (Stanley et al., 1996; Stanley et al., 2003). The competency of therapists in delivering NST-T will be assessed by Dr. Elizabeth Arnold and will be rated on a 0 to 8 scale, consistent with the CBT-T competency measure. Therapists who do not demonstrate competency (mean competency score < 6 for CBT-T or NST-T) will receive additional training and exposure to role play exercises until competency is demonstrated. Also, therapists must achieve 80% adherence across their sessions before contacting any potential participants. If a therapist fails to achieve this level, the PI will determine if there are specific components across sessions that are routinely omitted or implemented incorrectly and will retrain the therapist in the identified treatment components. Therapists will be randomly assigned to participants and will conduct all sessions for each participant. Supervisors will meet with the therapists weekly to discuss cases, review therapist

adherence and competence ratings, and answer any questions regarding the administration of the protocol. Any areas of nonadherence will be reviewed with the therapist. During this time, the therapist will have a chance to review any difficulties in the delivery of the intervention.

Randomization, data management, and quality control

Randomization will be stratified on baseline current depression diagnosis (major depression/dysthymia VS. no depression diagnosis), baseline psychotropic medication use, and therapist to assure balance between intervention groups on these important baseline characteristics.

Randomization protocol

We will use a permuted block algorithm (with random block lengths) to generate the randomization assignments for this study. Randomization will be executed via the secure web-based data management system, so that eligibility is automatically confirmed and records are current. This system will provide reports of expected follow-up sequences and missed appointments, will prevent withdrawal of participants after randomization has occurred, and will ensure concealment of the randomization scheme. To ensure masking of the assessment staff to intervention assignment, the randomization procedures will be performed by staff not involved in the assessments. When the randomization session is complete, an e-mail process will be spawned and a record of the transaction will be sent to the project manager and Dr. Brenes.

Data: quality control and security

We will use an internet-based, web browser application to manage screening, randomization, and follow-up visits. Entry into the web site is password-protected and encrypted. Data entry screens will be developed for collection of all data. Quality control reports will be generated in HTML, with a Cold Fusion to Oracle (a relational database management system) backend. The images on the data entry screens will mirror the data collection forms for ease and accuracy of entry. The Project Manager will review completed forms for accuracy and completeness. During data entry, key variables are checked for accuracy with the assigned range checks. Within our interactive data edit system, a review is required for any data entered outside of preset ranges. Override capabilities exist; however, overridden entries are flagged for review upon receipt by the data management staff. All computing systems are securely controlled in the Division of Public Health Sciences data center, which has limited access through badge access (with direct reporting to the Security office); it has environmental controls that monitor power, temperature, humidity and sound levels and triggers notifications to staff and engineering, who are on-call 24x7. The core infrastructure consists of multiple web servers, located in a secure network, behind a firewall, with multiple forms of intrusion detection systems to monitor incoming and outgoing traffic patterns and signatures to identify potentially dangerous unauthorized attacks. Analytical and database servers exist behind the firewall in the private network. All servers are backed up nightly and tapes are rotated between onsite storage and an offsite storage location. Web site users will be required to maintain secure passwords that change every 90 days.

Analyses

Analyses of Primary Outcomes. The focus of the primary analyses will be on the main effect of treatment and on the comparisons between the two interventions for each primary

outcome (HAM-A and PSWQ-A) 4 month follow-up measurements (Hypotheses 1 & 2). We will use a Bonferroni adjustment when carrying out these two comparisons. The first step in data analysis will be to examine descriptive statistics (means, standard deviations, minima, and maxima) and plots of the data (histograms for data measured only once and longitudinal plots of the data when possible) to become familiar with the data, examine for outliers, and examine for the necessity of data transformation (e.g., using the log, reciprocal, square root, or other transformation of the response or predictor variable). Order of priority in choosing a transformation will be to satisfy the 1) linearity assumption, 2) homogeneity assumption, and 3) normality assumption. Simple associations between variables will be estimated using Spearman's rank correlation coefficient. Comparisons of outcome measures (or transformations) between intervention groups will be made by mixed-model repeated measures analysis of covariance with an unstructured covariance matrix to account for the fact that multiple measurements (at approximately 2 months post-randomization, 4 months post-randomization, 9 months post-randomization, and 15 months post-randomization) from participants are not independent. Each primary hypothesis will be tested for the 4 month post-intervention measurement, using a contrast within the framework of this repeated measures analysis. In the primary analysis of intervention arms, all randomized subjects will be included in their original study group for analysis regardless of the final mode of intervention or the extent of compliance with the study protocol; that is, the primary analysis will follow an "intent to treat" philosophy. The analysis of covariance model for the primary outcomes will contain terms for the baseline value of the outcome, therapist (a factor to which participants are randomized), baseline current depressive disorder (used to stratify randomization), use of psychotropic medications at baseline (used to stratify randomization), the intervention effect, a time effect (at approximately 2 months post-randomization, 4 months post-randomization, 9 months post-randomization, and 15 months post-randomization), and the time by intervention interaction term. The interaction term is necessary in the model to allow the test of the primary hypothesis on the post-intervention measurement. Inclusion of outcomes collected at all follow-up time points will help make estimates unbiased in the situation where missing outcomes depend on outcomes observed at other time points. Additional secondary analyses will be performed to test between intervention groups for measurements at approximately 2 months post-randomization, 9 months post-randomization, and 15 months post-randomization. We will also perform a test of interaction between the therapist and intervention effect to explore if the therapist effect moderates the effect of the intervention.

Analysis of Secondary Outcomes. Secondary outcomes include results from the Beck Depression Inventory–Second Edition, the SF-36, the Pepper Center Tool for Disability, the Insomnia Severity Index, and the severity of GAD. Hypotheses 3-4 will be analyzed using mixed models repeated measures analysis of covariance using techniques like those described for Hypotheses 1-2. We will perform hypothesis tests at the 0.05 level for these outcomes and following the recommendations of Wang et al. (2007), we will report the overall probability of Type I error within published manuscripts.

Analysis of Moderators & Mediators. Pre-specified moderators of the effect of the intervention on the primary outcomes include age, gender, race, education, income, medical comorbidity, baseline current depression diagnosis, baseline severity of GAD, baseline psychotropic medication use, type of rural county (adjacent to metro area vs. not adjacent to

metro area), success of blinding, and therapist assignment. To the basic model used to test the primary intervention, we will add these baseline moderator variables and interaction terms between the potential moderators and the intervention effect. A separate model will be fit for each moderator variable and hypothesis tests of the interaction term will be used to determine if the baseline variable moderated the effect of the intervention on the primary outcomes. Analysis of potential mediators will be explored using considerations specific to randomized clinical trials reviewed by Kraemer et al. (2002). Mediators to be explored include medical services use, changes in psychotropic medication use, working alliance, patient satisfaction, adherence, and treatment credibility.

Human Subjects Protection

Informed Consent

Trained research assistants will provide full consent about the procedures of the study to all potential participants. Participants will be told that they may decline to participate or withdraw from the study at any time. They will be assured that their decision to give, withhold, or retract consent on this matter will not in any way influence their present or future care at Wake Forest University Health Sciences. In the context of obtaining informed consent, the limits of confidentiality in this study will be explained to participants. Specifically, confidentiality will be broken in only the following: a) if a participant is found to be imminently and planfully suicidal, b) if a participant is found to be homicidal, c) if a participant is suspected of committing child or elder abuse as defined by the statutes of North Carolina, or d) under a court-ordered subpoena. The research assistant will answer any questions that a potential participant may have. All participants will sign the informed consent prior to enrollment into the study. Participants will be given a copy of the informed consent form. If at a later time they have any questions, they will be told that they can contact the principal investigator and will be given her telephone number. Participants will also be informed that if they have any questions regarding their rights as research participants, they may contact the Office of Research at Wake Forest University School of Medicine. This telephone number will also be listed on the informed consent form.

Crisis Protocol

If any participant indicates a significant worsening in anxiety or depression scores (1) 1 standard deviation decline based on pilot data; 6.7 for PSWQ-A or 6.43 for the BDI-II, 2) BDI-II question 9 equals 2 or 3), the computer software system will automatically generate an e-mail to the PI and the project manager. If there is a need for immediate treatment (e.g., active suicidal ideation, active psychotic symptoms, disorientation, active substance abuse) at any point in time, the staff person will notify the PI. In both cases, the participant may be referred for psychiatric care.

As an additional safety precaution, we will ask each participant upon entry into the study to identify 2 persons whom we can contact in case of an emergency. All participants will receive information about safety precautions and procedures to follow in the event of a crisis (i.e., the participant becomes imminently suicidal). Each participant will be given telephone numbers for the WFUBMC psychiatrist-on-call and crisis hotline. Participants will be able to reach study staff and the psychiatrist-on-call 24-hours a day. If it is determined that a participant is not at risk of imminent harm, we will guide the participant to use coping skills from the treatment that

may apply and may refer them for additional psychiatric care. If a participant continues to report active suicidal ideation and is at imminent risk, we will ask if there is anyone at home with the participant, speak with them, and have them take the participant to the nearest emergency room for an immediate evaluation. If there is no one with the participant, study staff will contact the person's emergency contacts and instruct them to take the participant to the nearest emergency room for an immediate evaluation. If there is no one available to do this, mobile crisis management teams run by the county mental health system will be contacted (when available) and local law enforcement will be called to transport the participant to an emergency room. Because active suicidal ideation is an exclusion criterion for the study, we anticipate that the risk of participants becoming suicidal during the study will be minimal. Furthermore, based on our pilot study, no participants randomized into the study became imminently suicidal. All study staff (therapists, assessors, project manager) will receive training on the crisis protocol and will have regular weekly meetings with the team to discuss clinical issues.

Confidentiality and Privacy

Confidentiality will be protected by collecting only information needed to assess study outcomes, minimizing to the fullest extent possible the collection of any information that could directly identify subjects, and maintaining all study information in a secure manner. To help ensure subject privacy and confidentiality, only a unique study identifier will appear on the data collection form. Any collected patient identifying information corresponding to the unique study identifier will be maintained on a separate master log. The master log will be kept secure, with access limited to designated study personnel. Following data collection subject identifying information will be destroyed at the earliest opportunity, consistent with data validation and study design, producing an anonymous analytical data set. Data access will be limited to study staff. Data and records will be kept locked and secured, with any computer data password protected. No reference to any individual participant will appear in reports, presentations, or publications that may arise from the study.

Data and Safety Monitoring

As adverse event reports are collected, all adverse events will be identified and reported to the principal investigator. The principal investigator is responsible for the review of all adverse event reports and determining whether any changes in the study protocol or informed consent are required to insure subject safety and welfare. A compiled summary of all reported adverse events will be reviewed by the Data Safety and Monitoring Board on a semiannual basis and more frequently as needed. Additionally, any unanticipated problems, deviations, and protocol changes will be promptly reported by a member of the research team to the IRB.

Clinical Monitoring

The PI will meet with the study staff weekly to provide supervision and review the clinical status of all participants. Study staff will also notify at least one supervisor immediately if a patient shows the need for urgent treatment (e.g., suicidal intent, active psychosis). This type of information will be communicated immediately, with consultation about an appropriate course of action. The study statisticians will complete monthly reports indicating if any participants have a >1 standard deviation change for the worse in depressive symptoms.

Data Safety and Monitoring Board

The Data Safety and Monitoring Board will consist of Julie Wetherell, Ph.D. (chair of DSMB; UCSD), Pat Arean, Ph.D. (UCSF), and John Preisser, Ph.D. (UNC-Chapel Hill). These individuals will have primary responsibility for preparing the data and safety monitoring plan, ensuring that monitoring is timely and effective, and responding to recommendations and findings that emanate from monitoring activities. Monitoring will be performed throughout the proposed study via semiannual meetings. At each meeting, information regarding the number of participants entering the study, status with respect to meeting recruitment targets, percentage of patients assessed who enter the study, number of drop-outs, reasons for drop-out, percentage of patients at each stage of the project, and percentage of assessments completed at each assessment point. Information about any adverse events (adverse events will be reported in writing within 7 calendar days of any member of the investigative team becoming aware of such an event to the IRB) will be presented. By examining this information, the data and safety monitoring team will keep abreast of critical issues regarding recruitment and data integrity. Reports of all DSMB meetings and recommendations will be provided to the NIMH and WFUSM IRB.

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