Cultural and Linguistic Adaptation of a Telephone-Based Intervention to Treat Depression and Anxiety in Hispanic Cancer Survivors

Wake Forest Baptist Comprehensive Cancer Center
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Participating Institution(s):
Wake Forest University Health Sciences

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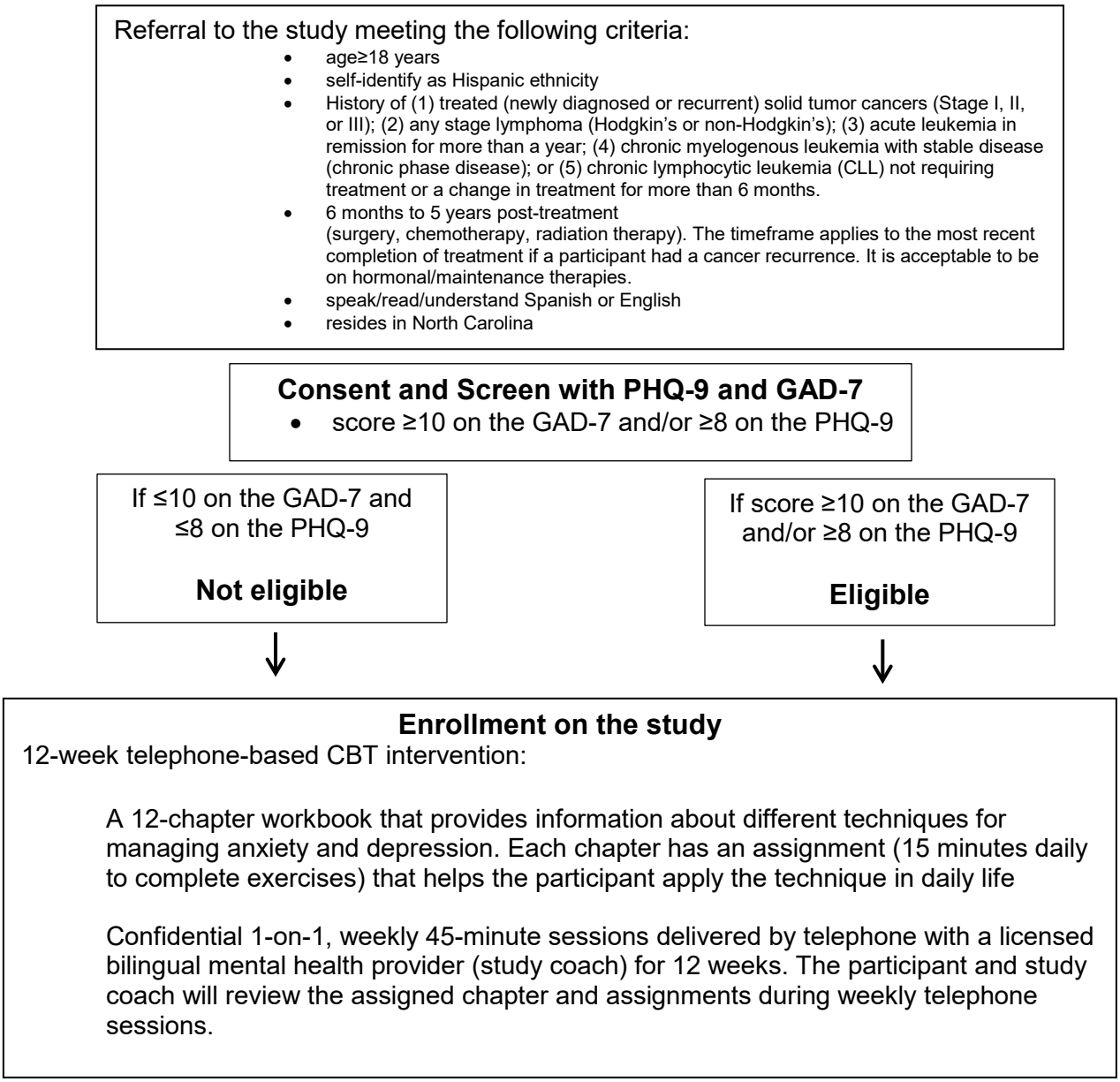
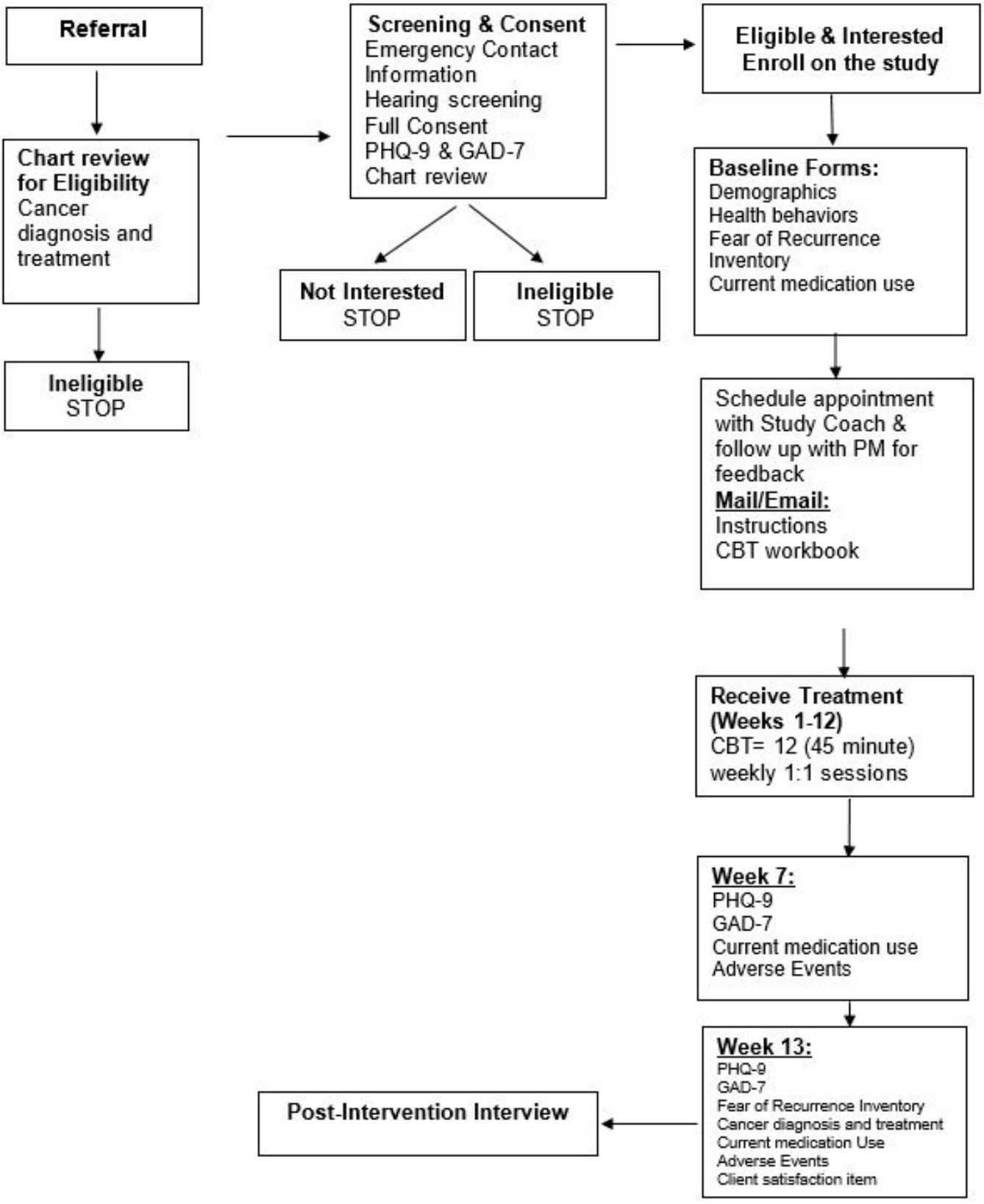

Referral to the study meeting the following criteria:
age≥18 years
self-identify as Hispanic ethnicity
History of (1) treated (newly diagnosed or recurrent) solid tumor cancers (Stage I, II, or III); (2) any stage lymphoma (Hodgkin's or non-Hodgkin's); (3) acute leukemia in remission for more than a year; (4) chronic myelogenous leukemia with stable disease (chronic phase disease); or (5) chronic lymphocytic leukemia (CLL) not requiring treatment or a change in treatment for more than 6 months.
6 months to 5 years post-treatment (surgery, chemotherapy, radiation therapy). The timeframe applies to the most recent completion of treatment if a participant had a cancer recurrence. It is acceptable to be on hormonal/maintenance therapies.
speak/read/understand Spanish or English
resides in North Carolina
Consent and Screen with PHQ-9 and GAD-7
score ≥10 on the GAD-7 and/or ≥8 on the PHQ-9
If ≤10 on the GAD-7 and ≤8 on the PHQ-9
Not eligible
If score ≥10 on the GAD-7 and/or ≥8 on the PHQ-9
Eligible
Enrollment on the study
12-week telephone-based CBT intervention:
A 12-chapter workbook that provides information about different techniques for managing anxiety and depression. Each chapter has an assignment (15 minutes daily to complete exercises) that helps the participant apply the technique in daily life
Confidential 1-on-1, weekly 45-minute sessions delivered by telephone with a licensed bilingual mental health provider (study coach) for 12 weeks. The participant and study coach will review the assigned chapter and assignments during weekly telephone sessions.


Referral
Chart review for Eligibility
Cancer diagnosis and treatment
Ineligible
STOP
Screening & Consent
Emergency Contact Information
Hearing screening
Full Consent
PHQ-9 & GAD-7
Chart review
Not Interested
STOP
Ineligible
STOP
Eligible & Interested
Enroll on the study
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Health behaviors
Fear of Recurrence Inventory
Current medication use
Schedule appointment with Study Coach & follow up with PM for feedback
Mail/Email:
Instructions
CBT workbook
Receive Treatment (Weeks 1-12)
CBT= 12 (45 minute) weekly 1:1 sessions
Week 7:
PHQ-9
GAD-7
Current medication use
Adverse Events
Week 13:
PHQ-9
GAD-7
Fear of Recurrence Inventory
Cancer diagnosis and treatment
Current medication Use
Adverse Events
Client satisfaction item
Post-Intervention Interview

1.0 Introduction and Background

Psychological concerns are among the most commonly reported unmet needs among post-treatment cancer survivors.[1] Up to 54% of post-treatment cancer survivors report clinically significant distress,[2,3] which is associated with multiple adverse outcomes, including mortality.[4,5] Hispanic cancer survivors have a disproportionately higher risk of experiencing anxiety and depressive symptoms relative to non-Hispanic whites,[6-11] even up to 5 years after diagnosis.[9] Further, Hispanic cancer survivors are less likely to receive psychosocial services than non-Hispanic whites.[12] Cognitive-behavioral therapy (CBT) has a large evidence base demonstrating its efficacy in reducing distress, [13] anxiety, [14,15] and depressive symptoms[14-21] among Hispanics.

The pilot work extends our current work by increasing our ability to serve a broader group of cancer survivors (including those who speak Spanish), addressing a disparity in supportive care services available to Hispanic cancer survivors. The work in this pilot grant targets the needs of Hispanic cancer survivors in our catchment area and broadens our ability to provide psychosocial care to Hispanic cancer survivors (regardless of language) by obtaining critical survivor and provider feedback to culturally adapt an existing evidence-based intervention.

2.0 Objectives

Building on this study team's current NCI-funded study of a telephone-based intervention targeting English-speaking rural cancer survivors (5R21CA198237, MPIs Danhauer/Brenes), this study proposes to culturally and linguistically adapt a telephone-based cognitive-behavioral therapy (CBT) intervention designed to reduce anxiety and depressive symptoms for use with Hispanic cancer survivors (Spanish- or English-speaking). Twelve participants will be recruited to participate in the tailored CBT intervention. They will provide content/process feedback on the intervention and undergo assessment of relevant future outcomes (to be used as pilot data). Participants with either moderate or severe distress (anxiety and/or depressive symptoms) will complete the telephone-based intervention that will consist of a CBT workbook with accompanying psychotherapy by a bilingual mental health provider. Each participant will choose whether (s)he prefers to complete the intervention in Spanish or English (at least half of the participants will complete the study in Spanish).

2.1 Primary Objectives

2.1.1 To assess the feasibility (participation, accrual, retention, adherence) of administering the intervention in Hispanic cancer survivors.

2.1.2 To culturally adapt an existing behavioral intervention for cancer survivors based on stakeholder feedback.

2.2 Exploratory Objectives

2.2.1 To summarize emotional distress (anxiety, depressive symptoms) and fear of recurrence in these post-treatment Hispanic cancer survivors.

2.2.2 To describe the therapy process in terms of satisfaction with treatment and the therapist-participant relationship.

3.0 Patient Selection

Participants with moderate or severe anxiety and/or depressive symptoms.

3.1 Inclusion Criteria

- Inclusion: age≥18 years;
- Self-identify as Hispanic ethnicity
- score ≥10 on the GAD-7 and/or ≥8 on the PHQ-9;
- History of (1) treated (newly diagnosed or recurrent) solid tumor cancers (Stage I, II, or III); (2) any stage lymphoma (Hodgkin's or non-Hodgkin's); (3) acute leukemia in remission for more than a year; (4) chronic myelogenous leukemia with stable disease (chronic phase disease); or (5) chronic lymphocytic leukemia (CLL) not requiring treatment or a change in treatment for more than 6 months.
- 6-60 months post-treatment (surgery, chemotherapy, and/or radiation therapy) for cancer (If only received active surveillance for prostate cancer or lymphoma with no other cancer treatment, participant is ineligible.) The timeframe applies to the most recent completion of treatment if a participant had a cancer recurrence. It is acceptable to be on hormonal/maintenance therapies.
- Must be able to speak, read, and understand Spanish or English
- Resides in North Carolina

3.2 Exclusion Criteria

- Current psychotherapy [regular appointment(s) with a mental health provider within the last 30 days]
- Self-reported active alcohol or substance abuse within the last 30 days
- Past history of prostate cancer or non-Hodgkin's lymphoma with only active surveillance (i.e., no surgery, chemotherapy, or radiation therapy)
- Progressive cancer
- Global cognitive impairment based on self-reported diagnosis of dementia.
- Self-reported psychotic symptoms in the last 30 days (Item in Screening Form: "Have you seen things that aren't really there or have you heard voices when no one else was around within the last 30 days?")
- Active suicidal ideation with plan and intent
- Any change in psychotropic medications within the last 30 days
- Hearing loss that would preclude participating in telephone sessions (determined by brief hearing assessment administered by research staff). *Individuals who can compensate for hearing loss through the use of a hearing device or TDD phone, and through the use of such devices are able to communicate with the study therapist by telephone, will be included. If the therapist cannot communicate with the participant by telephone, the participant will be excluded.*
- Failure/inability/unwillingness to provide names and contact information for two family members or friends to serve as emergency contacts during the course of the study

3.3 Inclusion of Women and Minorities

Both men and women are eligible for this open pilot trial. The entire sample (N=12) will be Hispanic because this is our target population. Children will not be included because the research topic is not relevant to children. While children may experience depression and/or anxiety, the treatment approach would be different from the approach used in this study that has been developed for use with adults.

4.0 Registration Procedures

All patients entered on any WFBCCC trial, whether treatment, companion, or cancer control trial, **must** be linked to the study in EPIC within 24 hours of Informed Consent. Patients **must** be registered prior to the initiation of treatment.

You must perform the following steps in order to ensure prompt registration of your patient:

1. Complete the Eligibility Checklist (Appendix A)
2. Complete the Protocol Registration Form (Appendix B)
3. Alert the Cancer Center registrar by phone, *and then* send the signed Informed Consent Form, Eligibility Checklist and Protocol Registration Form to the registrar, either by fax or e-mail.

   Contact Information:
   Protocol Registrar PHONE (336) 713-6767
   Protocol Registrar FAX (336) 713-6772
   Protocol Registrar E-MAIL (registra@wakehealth.edu)

   *Protocol Registration is open from 8:30 AM - 4:00 PM, Monday-Friday.

4. Fax/e-mail ALL eligibility source documents with registration. Patients **will not** be registered without all required supporting documents.

Note: If labs were performed at an outside institution, provide a printout of the results. Ensure that the most recent lab values are sent.

To complete the registration process, the Registrar will register the patient on the study.

5.0 Study Outcomes and Study Measures

Participants will have the choice to complete all study measures in either English or Spanish.

Data Collection -- Self-Report (Qualitative) Measures. The research staff will obtain weekly feedback on the process and content of the intervention in brief (~5 minute) phone calls following the weekly telephone sessions. Study staff will also complete telephone assessments at baseline (Week 0), halfway through the intervention (Week 7), and upon completion of the intervention (Week 13). Additionally, upon completion of the intervention, a Q-PRO staff person will conduct a semi-structured in-depth interview designed to identify any issues (logistical, intervention feedback, feedback on how the process/content could work better for Hispanic cancer survivors) and maximize usability of the CBT workbook. These interviews will last up to 60 minutes and be conducted over the phone. Interviews will be recorded with participants' permission and then

summarized. After the first 4 participants complete the intervention and in-depth interview, Q-PRO and the MPIs will review the data. Suggested changes will be made to the intervention and tested in the next 4 participants. Remuneration for time will be provided.

5.1 Primary Outcomes

5.1.1 **Feasibility** (participation, accrual, retention, adherence rates)

To determine study feasibility, recruitment, accrual, retention, and adherence rates, which will be calculated as follows:

Participation. To determine participation rate, we will track the total number of individuals approached, the number of individuals who met all eligibility criteria, and percent who agree to participate.

Accrual. Accrual rates will be calculated by calculating the mean number of participants recruited per month.

Retention. Study retention will be estimated by the proportion of participants who complete the Week 13 visit. Drop-out is defined as 100% minus the dropout %.

Adherence. Intervention adherence will be estimated as the mean percentage of therapy or check-in sessions each participant completes. Participants must complete at least 9 of the 12 sessions (75%) to be considered adherent.

5.2 Secondary Outcomes

5.2.1 Anxiety – GAD-7

The **GAD-7**[53] is a self-report measure of DSM-IV symptoms of GAD. Participants rate 7 questions on a scale of 0 (not at all) to 3 (nearly every day); one additional question assesses the interference of these symptoms with functioning. The first 7 questions are summed to create a total score. It has been validated for use in the general population[70] and in primary care.[53] The GAD-7 has demonstrated good sensitivity (89%) and specificity (82%) in identifying GAD diagnoses when using a cut point of 10.[53] It also has good internal consistency (alphas = 0.89-0.92) and test-retest reliability (intraclass correlation = .83).[53,70]

5.2.2 Depressive Symptoms – PHQ-9

The **PHQ-9** is a self-report measure of DSM-IV symptoms of Major Depressive Disorder. Participants rate how often they have experienced nine symptoms over the past 2 weeks on a scale of 0 (not at all) to 3 (nearly every day). Responses are summed, with higher scores indicating greater depressive symptomatology. It has demonstrated good reliability and validity. The traditional cutoff for the PHQ-9 is a score ≥10. However, ASCO guidelines recommend using a score ≥8, based on a study of cancer outpatients[76] and a meta-analysis of use of the PHQ-9 for identifying depression in cancer patients.[77]

5.2.3 Fear of Recurrence – Fear of Recurrence Inventory Severity Subscale

The **Fear of Cancer Recurrence Inventory**[55] (FCRI; severity subscale) will be used to measure self-reported fear of recurrence. This 9-item subscale measures the presence and severity of the intrusive thoughts or images associated with the fear of recurrence, and it can be used separately as a short form of the 42-item FCRI for the brief screening of fear of cancer recurrence. The measure is widely used and has strong reliability and validity (Cronbach's α=0.75).

6.0 Intervention Plan

Participants will have the choice to complete the intervention in either English or Spanish.

Intervention Adaptation. Building on the feedback received from Aim 1 from key clinical, bilingual psychotherapist, and patient stakeholders (IRB00063774), we will iteratively refine the CBT workbook based on feedback from 12 cancer survivors receiving the intervention and completing relevant outcome and feasibility measures.

Intervention. Participants with moderate or severe anxiety and/or depressive symptoms will participate in the telephone-based intervention that consists of the CBT workbook (15 minutes daily to complete exercises), plus psychotherapy delivered by telephone with a licensed bilingual mental health provider (45-50 minute sessions weekly). Two therapists who meet the following requirements have been hired to conduct the intervention. They meet the following qualifications: Master's or doctoral degree in counseling, marriage and family therapy, psychology, or social work; licensed as an independent mental health provider in North Carolina; and experience with CBT. The therapists will complete study-specific training with Dr. Brenes that will cover study design, anxiety/depression in cancer survivors, principles of CBT, intervention delivery, and use of the workbook. The professionally-prepared CBT workbook focuses on cognitive-behavioral techniques for managing anxiety, depression, and distress. Chapters focus on the cognitive-behavioral model of depression and anxiety, relaxation techniques, cognitive restructuring, problem solving, worry control, exposure, behavioral activation, and relapse prevention. Workbook chapters target issues specific to cancer survivors, such as (a) fear of recurrence;[2,3,29-41] (b) lasting effects of treatment on health, ongoing symptoms of fatigue and physiologic effects of cancer treatment;[2,3,29,32,37,41,42] (c) late effects of cancer treatment (the possibility of developing other diseases);[29,38,43] (d) concerns about reproductive ability[42,44] and (e) distress related to changes in body image and sexuality.[31,38,43] The sessions will supplement the participant's understanding of distress management techniques and include a review of the daily workbook exercises to assure understanding and maximize application in daily life.

6.1 Study-Related Flow Activities

Screening and Consent Procedures

Patients will be referred from oncology providers and the Hispanic patient navigator or from the community.

Pre-Visit

We will obtain a limited HIPAA waiver to assess the potential participant's name, contact information, and demographics. This information will be collected on a Pre-Visit Form that will be reviewed with potential participants during the screening phone contact to assess for eligibility.

Informed Consent

After making sure the patient clearly understands the study procedures and agrees to follow them, the patient will be asked to sign the informed consent form electronically (e.g., REDCap) or in person. If signed electronically, REDCap will allow the study team to access signed electronic consent forms immediately after signature. Patients will have the option to download a copy of the signed informed consent from REDCap, or a hard copy will be provided to the patient if needed.

Screening

The screening process will occur by telephone. Once a participant has signed the informed consent, emergency contact information will be collected and the participant will be screened for adequate hearing ability and additional screening criteria. The PHQ-9 and GAD-7 will be administered. If the participant is eligible based on the scoring of the PHQ-9 and GAD-7, then additional screening questions will be administered.

The Screening Form will be reviewed with participants to confirm contact information, demographics, and chart information (eligibility criteria – type of cancer, month/year of diagnosis, cancer stage at time of diagnosis, time of last treatment, date of birth). Additional questions will also be administered to assess additional eligibility criteria including an item to determine adequate hearing ability (please refer to the next paragraph for additional hearing ability information), telephone access, and language preference.

To determine adequate hearing ability, the participant is asked to repeat the phrase, "I have a cat so all I need is a dog." If the participant is able to repeat this phrase correctly, staff will continue with screening. If the participant is unable to repeat the phrase correctly after a second attempt or if staff thinks hearing is a problem, the participant will be considered ineligible and will not be screened further. Participants with a circumstance that could affect the ability to hear at the time of the call (illness, hearing aid problem, in process of obtaining hearing aid, etc.) can reschedule.

We will also collect information from the participant's medical chart, including type of cancer, month/year of diagnosis, cancer stage at time of diagnosis, time of last treatment.

If a participant is not eligible or declines study participation at screening, screening information will be entered into RedCap up to the point the participant was no longer eligible or declined, and no further information will be collected.

Baseline Testing

If informed consent was administered by electronically/by phone, the site must receive the signed full informed consent prior to initiating baseline study activities. Baseline interviewer-administered measures and chart review must be administered and completed by study staff. Baseline measures may be completed over the phone with study staff or through REDCap. The baseline measure responses must be received within 30 days after screening with PHQ-9 and GAD-7. Replacement packets can be emailed at

participant request. Study staff must receive the following self-administered completed forms from the participant prior to enrolling the participant.

Baseline Measures:

- Demographics
- Fear of Recurrence Inventory--Severity Subscale

Interviewer Administered Measures and Chart Review:

Research staff will administer the following forms (see Appendices) by telephone (or in person if participant is in clinic) and enter the data in REDCap **within 48 hours. These forms are to be interviewer-administered whether the contact is by telephone or in person. The PHQ-9 and GAD-7 should have no missing data.**

- PHQ-9 (administer *only* if it has been >30 days since screening to reassess eligibility)
- GAD-7 (administer *only* if it has been >30 days since screening to reassess eligibility)
- Current Medication Use

Chart Review:

- Initial Cancer Diagnosis and Treatment Form
- Additional Malignancy Diagnosis and Treatment Form
- Cancer Relapse/Recurrence Form

Weekly

The study staff will obtain weekly feedback on the process and content of the intervention and completion of the study measures in brief (5-10 minutes) phone calls following the intervention sessions. The Project Manager will work to coordinate calls shortly after the end of weekly therapy sessions and enter responses into REDCap.

Weeks 7 and 13:

The participant will complete questionnaires and telephone interviews during week 7 and week 13 of the study. During week 7, the participant will complete the PHQ-9 and GAD-7. Study staff will obtain information about current medication use and adverse events. At week 13, patients will again complete the PHQ-9, GAD-7, Fear of Recurrence Inventory--Severity Subscale, client satisfaction item. Study staff will obtain information about cancer diagnosis and treatment information, current medication use, and adverse events.

After completing the intervention, a Q-PRO staff person will conduct a semi-structured in-depth interview designed to identify any issues (logistical, intervention feedback, feedback on how the process/content could work better for Hispanic cancer survivors) and maximize usability of the CBT workbook. Interviews will last up to 60 minutes and be conducted via telephone. Interviews will be recorded and summarized. After the first 4 participants, Q-PRO and the MPIs will review the data. Changes will be made and tested in the next 4 participants. Remuneration for time and transportation will be provided. Individuals who are unable to afford a telephone may be provided with assistance to cover this expense. This will be determined on a case-by-case basis.

Participant Enrollment

The participant should not be enrolled until the participant is ready to start the intervention. Once the participant is enrolled, the study timeline begins.

Table 3. Study Measures[a]	Screen	Baseline Wk 0	Mid Wk 7	Post Wk 13
Eligibility Items	X			
Hearing Screen	X			
Emergency Contacts	X			
Depressive Symptoms - PHQ-9[25,26]	X		X	X
Anxiety Symptoms - GAD-7[27]	X		X	X
Demographic		X		
Fear of Recurrence Inventory Severity Subscale[28]		X		X
Cancer Diagnosis & Treatment Information		X		X
Current Medication Use		X	X	X
Adverse Event (AE) Form		Complete as needed		
AE Ascertainment Form			X	X
Intervention Feedback			Weekly (Wks 1-12)	
Post-Intervention Interview				X
Client Satisfaction Item				X
Progress Notes/Session Information Form			Weekly (Wks 1-12)	
Participant Status Change Form			Complete as needed	

[a]Ideally all assessments will be completed within 2 weeks of when they are due, but **must** be completed within 6 weeks of the time that they are due

6.2 Supportive Care Guidelines-Crisis Protocol

Anxiety is measured by the GAD-7 at baseline and weeks 7 and 13. Depression is measured by the PHQ-9 at baseline and at weeks 7 and 13. When the data from either of these two forms are filled out, the study staff will document the scores to ensure participants have not indicated a significant worsening in anxiety or depression scores (1 standard deviation increase [rounded to the nearest integer) on the GAD-7 (Change≥4)[75] or PHQ-9 (Change≥6)[73] from baseline]. If there has been a significant change, the Project Manager will initiate the Crisis Protocol and complete a Crisis Protocol Event Form. During the course of a regularly scheduled participant contact, it may become evident that there is a need for immediate evaluation (e.g., active suicidal ideation, active psychotic symptoms, disorientation). Staff will be instructed to follow the Crisis Protocol and complete the Crisis Protocol Event Form. In both cases, the participant may be referred for mental health care by their primary care physician or by an emergency department physician.

Study staff will follow the steps outlined in the Crisis Protocol and participants will receive information about safety precautions and procedures to follow in the event of a crisis (i.e., the participant becomes imminently suicidal). 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. Further, in our prior studies, no participants randomized into the study became imminently suicidal. All study staff (therapists, research staff) will receive training on the Crisis Protocol and coping with participant distress that may be experienced during the consent, assessment and treatment procedures. In addition, there will be regular study team meetings to discuss clinical issues. Dr. Brenes will review the status and progress of participants with the study therapists on a regular (at least monthly) basis. All participants will be contacted at Week 7 and Week 13 to assess the primary outcomes and depressive

symptoms. Additionally, study therapists will attempt to reach participants who miss a session by calling the participant twice in a one-week period. If the therapist is unable to contact the participant by phone, the therapist will send the participant a letter with a request that the participant contact the therapist regarding interest in continuing the study sessions.

6.3 Duration of the Intervention

CBT Intervention. CBT will consist of 12 individual weekly psychotherapy sessions with a study therapist by telephone and an accompanying workbook. We have used this treatment in 4 previous RCTs. The 12-chapter workbook focuses on techniques that have demonstrated efficacy in treating adults with an anxiety disorder and is currently being used in an ongoing for rural post-treatment cancer survivors.[45,4647-51]

All participants receive 12 identical chapters according to their language preference. To tailor the intervention to anxiety and depressive symptoms, participants are instructed to choose 2 chapters from a menu of 5 chapters (e.g. pain, more focused information on changing behavior related to anxiety or depression, etc.). Workbook chapters target issues specific to cancer survivors, such as (a) fear of recurrence (most commonly reported source of distress in survivors across different types of cancer);[8,9,13,24,38–48] (b) lasting effects of treatment on health, ongoing symptoms of fatigue and physiologic effects of cancer treatment;[38,39,42,44,48–50] (c) late effects of cancer treatment (the possibility of developing other diseases);[14,38,45] (d) concerns about reproductive ability and higher risk of cancer for their children;[50,51] and (e) distress related to changes in body image and sexuality.[14,41,45]

There will be weekly telephone sessions with the study therapist that will last 45 to 50 minutes. The participant and therapist will review the assigned chapter and assignments during weekly telephone sessions. In order to ensure privacy, every participant will be asked if he/she needs to reschedule the appointment due to a lack of privacy.

Coach training and supervision. Study coaches will be bilingual licensed mental health providers who have the ability to conduct therapy in both English and Spanish. Training will include use of the treatment manual, didactic presentations, readings, and role plays. The competency of coaches in delivering CBT-T will be evaluated with a measure developed and used by Dr. Melinda Stanley.[47,48] Coaches who fail to demonstrate competency (mean competency score < 6 on a scale of 1 to 8) will receive additional training and exposure to role play exercises until competency is demonstrated. Also, coaches must achieve ≥80% adherence across the sessions before contacting any potential participants. If any coach 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 coach in the identified treatment components. The PI will meet with the coaches weekly to discuss cases, review adherence and competence ratings, and answer any questions regarding the administration of the protocol. Any areas of non-adherence will be reviewed with the coaches.

6.4 Duration of Follow Up

Participants will be involved in a 12-week intervention and will complete the follow-up assessment immediately upon completion of the intervention.

6.5 Criteria for Removal from Study

Participants will be removed from study for the following reasons: the protocol intervention and any protocol-required follow-up period is completed, serious adverse event, lost to follow-up, withdraw consent, PI removes from study, or death. Participants also have the option to discontinue the intervention but continue in the study for follow-up purposes. For subjects who are enrolled, site staff must contact the subject at the next study visit with at least 5 attempts. After 5 documented contact attempts the subject will be considered lost to follow-up. Site staff must complete a Participant Status Change Form in RedCap.

7.0 Adverse Events List and Reporting Requirements

REPORTING ADVERSE AND SERIOUS ADVERSE EVENTS

Reportable Adverse Events
An adverse event (AE) is defined as any untoward or unfavorable medical occurrence in a human subject, including any clinically significant abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research. The burden of collecting and reporting data on every possible AE is excessive and therefore, study staff will report all serious adverse events (SAEs) and selected described below.

SAEs and AEs will be ascertained by study staff for all participants at Weeks 7 and 13. Study staff will administer the Adverse Event Ascertainment Form to specifically query participants about safety events at weeks 7 and 13. In addition, adverse events may also be reported to study staff spontaneously through telephone calls, emails or other correspondence. In addition to local reporting requirements, all SAEs and selected AEs will be recorded on the Adverse Event Form by clinic staff.

AEs will be assessed according to the grade associated with the CTCAE term. AEs that do not have a corresponding CTCAE term will be assessed according to the general guidelines for grading used in the CTCAE v5.0.. A copy of the CTCAE can be found at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

Serious Adverse Events

Definition: Regulations at 21 CFR §312.32 (revised April 1, 2014) define an SAE as any untoward medical occurrence that at any dose or intervention level has one or more of the following outcomes:
A Serious Adverse Event (SAEs) is defined if it results in ANY of the following outcomes:

- Death
- Life-threatening
- Results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24hours
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect

- Important Medical Event (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

Reporting Requirements for above Study Descriptions:

- All unexpected hospitalizations regardless of grade
- All Grade 5 toxicities (deaths-expected and unexpected)
- All unexpected Grade 4 toxicities
- All additional reporting requirements as outlined in the protocol

Selected Adverse Events

A select list of adverse events include suicide attempts, psychosis, worsening anxiety, worsening depression, and suicidal ideation, should be reported as an adverse event, regardless of whether they resulted in an ER visit or hospitalization.

Definition of Worsening Anxiety or Depression

An adverse event form should be completed for any participant who indicates a significant worsening in anxiety or depression scores (1 standard deviation increase (rounded to the nearest integer) on the GAD-7 (Change≥4) [75] or PHQ-9 (Change≥6)[73,74,51] from baseline). If there is a need for immediate treatment (e.g., active suicidal ideation, active psychotic symptoms, disorientation, and active substance abuse) at any point in time, staff persons will notify the co-PIs. In both cases, the participant may be referred for psychiatric care.

Data and Safety Monitoring: As adverse event reports are collected, all adverse events will be identified and reported to the co-principal investigators. The co-principal investigators are 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.

Clinical Monitoring: The co-PIs 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 Data Safety Monitoring Committee (DSMC) is responsible for reviewing SAEs for WFBCCC Institutional studies as outlined in Appendix D. All Adverse Events that occur during protocol intervention and are coded as either 1) unexpected grade 4, 2) unplanned inpatient hospitalization ≥ 24 hours (regardless of grade), or grade 5 (death) must be reported to the DSMC using the using the SAE console in WISER.

All WFBCCC Clinical Protocol and Data Management (CPDM) staff members assisting a Principal Investigator in investigating, documenting and reporting an SAE qualifying for DSMC reporting are responsible for informing a clinical member of the DSMC as well as the entire committee via the email notification procedure of the occurrence of an SAE.

8.0 Data Management

The PHQ-9 and GAD-7 must be entered into RedCap within 48 hours of being administered. The Crisis Protocol form must be entered into RedCap at the time the form is completed with the participant. All other assessments must be completed within the designated study visit windows then data entered into RedCap by designated site staff or designated study therapist within 14 days from the date assessments are completed.

Informed consent document	EPIC
Protocol registration form	WISER/OnCore
Depressive Symptoms - PHQ-9[25,26]	RedCap
Anxiety Symptoms - GAD-7[27]	RedCap
Demographic Information	RedCap
Fear of Recurrence Inventory Severity Subscale[28]	RedCap
Cancer Diagnosis & Treatment Information	RedCap
Current Medication Use	RedCap
Adverse Event (AE) Form	WISER/OnCore
AE Ascertainment Form	RedCap
Client Satisfaction Item	RedCap
Weekly Intervention Feedback	RedCap
Post-Intervention Interview	Files on a Secure Server
Progress Notes/Session Information Form	RedCap
Participant Change Status Form	RedCap

9.0 Statistical Considerations

9.1 Analysis of Primary Objective

Objective 2.1.1will provide data on feasibility, including participation, accrual, adherence, and retention rates. We will calculate 95% confidence intervals for each feasibility measure to determine the range of estimates consistent with our data. We will track the number approached for screening, number screened, number eligible, and the percent who agree to participate. For those not meeting eligibility criteria, reasons will be summarized. The proportion of participants and corresponding 95% CI for participants who participated in the intervention sessions and those who completed all assessments will be computed; we will also calculate the percent who complete the Week 13 visit to assess retention. We will use one-sample tests of binomial proportions to compare participation, adherence, and retention rates to the hypothesized values of 50%, 75%, and 75%, respectively.

Qualitative Analyses. Interview transcripts and field notes will be reviewed independently by two staff members of the Q-PRO Shared Resource who will provide an integrative summary/synthesis of the interviews (identification of key points, potential themes, areas needing further exploration). The qualitative and quantitative analyses will be evaluated in a mixed-methods framework for consistency and discrepancies to refine the intervention for future studies.

9.2 Analysis of Secondary Objective

8.2.1 Analysis of Exploratory Objectives

In exploratory analyses, we will summarize the variables of interest (anxiety, depressive symptoms) fear of recurrence, satisfaction, and the therapist-participant relationship) by visit using descriptive statistics. Because this is a small pilot study, this information will be used to estimate variability for future study planning purposes, but not to estimate effect size or to test hypotheses, and the analyses will be considered exploratory.

9.3 Sample Size Justification

An N=12 sample size is quite standard for qualitative analyses to achieve thematic saturation. With 12 people, we will be able to calculate two-sided 95% confidence intervals around proportions of interest within 28%. Power is not applicable for this study in the absence of hypothesis testing.

9.4 Estimated Accrual Rate

We will enroll 12 participants over six months at a rate of 2 participants per month.

9.5 Estimated Study Length

The study will span one year in duration.

9.6 Interim Analysis Plan

None planned.

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Appendix A – Eligibility Checklist

IRB Protocol No.	**WFBCCC Protocol No.**
Study Title: Cultural and Linguistic Adaptation of a Telephone-Based Intervention to Treat Depression and Anxiety in Hispanic Cancer Survivors	
Principal Investigators: Suzanne Danhauer, PhD & Gretchen Brenes, PhD	

Inclusion Criteria (as outlined in study protocol)	**Criteria is met**	**Criteria is NOT met**	**Source Used to Confirm * (Please document dates and lab results)**
Age≥18 years;	☐	☐	
Self-identify as Hispanic ethnicity	☐	☐	
Score ≥10 on the GAD-7 and/or ≥8 on the PHQ-9;	☐	☐	
History of (1) treated (newly diagnosed or recurrent) solid tumor cancers (Stage I, II, or III); (2) any stage lymphoma (Hodgkin's or non-Hodgkin's); (3) acute leukemia in remission for more than a year; (4) chronic myelogenous leukemia with stable disease (chronic phase disease); or (5) chronic lymphocytic leukemia (CLL) not requiring treatment or a change in treatment for more than 6 months.	☐	☐	
6-60 months post-treatment (surgery, chemotherapy, and/or radiation therapy) for cancer (If only received active surveillance for prostate cancer or lymphoma with no other cancer treatment, participant is ineligible.) The timeframe applies to the most recent completion of treatment if a participant had a cancer recurrence. It is acceptable to be on hormonal/maintenance therapies.	☐	☐	
Must be able to speak, read, and understand Spanish or English	☐	☐	
Resides in North Carolina	☐	☐	
Exclusion Criteria (as outlined in study protocol)	**Criteria NOT present**	**Criteria is present**	**Source Used to Confirm * (Please document dates and lab results)**
Current psychotherapy [regular appointment(s) with a mental health provider within the last 30 days]	☐	☐	

Self-reported active alcohol or substance abuse within the last 30 days	☐	☐	
Past history of prostate cancer or non-Hodgkin's lymphoma with only active surveillance (i.e., no surgery, chemotherapy, or radiation therapy)	☐	☐	
Progressive cancer	☐	☐	
Global cognitive impairment based on self-reported diagnosis of dementia.	☐	☐	
Self-reported psychotic symptoms in the last 30 days (Item in Screening Form: "Have you seen things that aren't really there or have you heard voices when no one else was around within the last 30 days?")	☐	☐	
Active suicidal ideation with plan and intent	☐	☐	
Any change in psychotropic medications within the last 30 days	☐	☐	
Hearing loss that would preclude participating in telephone sessions (determined by brief hearing assessment administered by research staff). *Individuals who can compensate for hearing loss through the use of a hearing device or TDD phone, and through the use of such devices are able to communicate with the study therapist by telephone, will be included. If the therapist cannot communicate with the participant by telephone, the participant will be excluded.*	☐	☐	
Failure/inability/unwillingness to provide names and contact information for two family members or friends to serve as emergency contacts during the course of the study	☐	☐	

This subject is ☐ eligible / ☐ ineligible for participation in this study.

OnCore Assigned PID: ___ ___ ___ ___ ___ ___ ___ ___ ___

Signature of research professional confirming eligibility: _____

Date: _____/_____/_____

Appendix B – Protocol Registration Form

DEMOGRAPHICS

Patient: Last Name: _____ First Name: _____

MRN: ___ ___ ___ ___ ___ ___ ___ ___ DOB (mm/dd/yy): ___ ___ / ___ ___ / ___ ___

ZIPCODE: ___ ___ ___ ___ ___

SEX: ☐ Male ☐ Female Ethnicity (choose one): ☐ Hispanic

☐Non-Hispanic

Primary Diagnosis: _____

Date of Diagnosis: ___ ___ /___ ___/___ ___

PROTOCOL INFORMATION

Date of Registration: ___ ___ / ___ ___ / ___ ___

MD Name (last) : _____

Date protocol treatment started: ___ ___ / ___ ___ / ___ ___

Informed written consent: ☐ YES ☐ NO

(consent must be signed prior to registration)

Date Consent Signed: ___ ___ / ___ ___ / ___ ___

PID # (to be assigned by OnCore): ___ ___ ___ ___ ___ ___ ___ ___ ____

Protocol Registrar can be contact by calling 336-713-6767 between 8:30 AM and 4:00 PM, Monday – Friday.

Compete the eligibility checklist in WISER and then give the completed Eligibility Checklist and Protocol Registration Form must be hand delivered, faxed or e-mailed to the registrar at 336-713-6772 or registra@wakehealth.edu, respectively.

Appendix C – STRC Reporting Requirements

Data and Safety Monitoring Committee (DSMC) Serious Adverse Event (SAE) Notification SOP	**Date: 02/11/2021**

Mandatory DSMC SAE Reporting Requirements in WISER

This document describes reporting requirements of adverse events from **WFBCCC Investigator Initiated interventional trials to the Data and Safety Monitoring Committee (DSMC).** A trial is considered a **WFBCCC Investigator Initiated interventional trial** if the following criteria are met:

1) The Principal Investigator (PI) of the trial is a member of a department at the Wake Forest University Baptist Medical Center.
2) WFBCCC is considered as the primary contributor to the design, implementation and/or monitoring of the trial.
3) The trial is designated as "Interventional" using the Clinical Research Categories definitions provided by the NCI in the Data Table 4 documentation. (https://cancercenters.cancer.gov/GrantsFunding/DataGuide#dt4)

There are two distinct types of WFBCCC Investigator Initiated interventional trials based on where patient enrollment occurs. These include:

1) Local WFBCCC Investigator Initiated interventional trials defined as trials where **all patients are enrolled from one of the WFBCCC sites.** These include the main outpatient Cancer Center clinics (located in Winston-Salem) as well as WFBCCC affiliate sites located in Bermuda Run (Davie Medical Center), Clemmons, Lexington, High Point, or Wilkesboro.
2) Multi-Center WFBCCC Investigator Initiated interventional trials defined as trials where patients are enrolled from other sites in addition to WFBCCC sites.
   There are three types of trials that are included in this category:
   a. Trials sponsored by the NCI Community Oncology Research Program (NCORP) that are conducted at multiple sites where the PI is a member of a department at the Wake Forest University Baptist Medical Center.
   b. Trials sponsored by Industry that are conducted at multiple sites and the PI is a member of a department at the Wake Forest University Baptist Medical Center.
   c. Trials sponsored by WFBCCC that are conducted at multiple sites and the PI is a member of a department at the Wake Forest University Baptist Medical Center.

All Adverse Events (AEs) and Serious Adverse Events (SAEs) that occur on any patients enrolled on WFBCCC Investigator Initiated Interventional trials must be entered into the WISER system. The only exception to this requirement is for patients enrolled on NCORP trials at non- WFBCCC sites. AEs and SAEs for NCORP patients enrolled at WFBCCC sites must be entered into the WISER system. Once these AEs and SAEs are entered in WISER, certain actions must be taken regarding the reporting of specific Adverse Events to the DSMC.

All Adverse Events that occur during protocol intervention (defined below) and are coded as either 1) **unexpected grade 4,** 2) **unplanned inpatient hospitalization ≥ 24 hours (regardless of grade)**, or **grade 5 (death)** must be reported to the DSMC to the using the using the SAE console in WISER.

A research nurse or clinical research coordinator when made aware that an adverse event meets one of the above criteria has occurred on a WFBCCC Investigator Initiated interventional trial, is responsible for informing a clinical member of the DSMC by phone (or in-person) about the adverse event. The nurse/coordinator should contact the treating physician prior to calling the DSMC clinical member to obtain all details of the SAE, as well as all associated toxicities to be recorded along with the SAE. In addition, this nurse or coordinator is responsible for entering the adverse event information into the SAE console in WISER. Once the adverse event has been entered into the SAE console an email informing the entire DSMC will be generated.

THESE REPORTING REQUIREMENTS APPLY TO any staff member on the study team for a WFBCCC Institutional Interventional trial. Ultimately, the protocol PI has the primary responsibility for AE identification, documentation, grading and assignment of attribution to the investigational agent/intervention. However, when an AE event as described above is observed, it is the responsibility of the person who observed the event to be sure that it is reported to the DSMC.

What is considered during protocol intervention?
During protocol intervention is considered to be the time period while a patient is on study treatment or during the time period within 30 days of last study treatment (even if patient begins a new (non-study) treatment during the 30 days). This window of 30 days should be the standard window to be used in all protocols unless a specific scientific rationale is presented to suggest that a shorter window can be used to identify events. If it is a trial sponsored by Industry and the sponsor requires a longer window for monitoring of SAEs, then the longer window of time specified by the sponsor should be followed.

What is considered as an Unexpected Grade 4 event?
Any grade 4 event that was not specifically listed as an expected adverse event in the protocol should be considered as unexpected. A grade 4 adverse event can be considered to be unexpected if it is an event that would not be expected based on the treatment being received or if it is unexpected based on the health of the patient. In either case, if there is any uncertainty about whether a grade 4 adverse event is expected or unexpected it should be reported to DSMC.

DSMC notification responsibilities of the person (e.g., nurse) handling the reporting/documenting of the SAE in WISER:

1. Make a phone call (or speak in person) to the appropriate clinical member of the DSMC according to the schedule as listed below (page if necessary).
2. Enter a new SAE into the SAE module that is located in the Subject>> CRA Console in WISER WITHIN 24 HOURS of first knowledge of the event. Information can be entered and saved, but the DSMC members will not be notified until a date is entered into the DSMC Notification Date Field. This will ensure that all persons that need to be made aware of the event (i.e., PI, study team members and DSMC members) will be notified; remember to file a copy of the confirmation.
3. Document that the appropriate person(s) on the DSMC has been contacted. Indicate the name of

the DSMC clinician that was contacted and the date and time contacted in the Event Narrative field in the SAE console of the particular subject.

4. Document whether or not the protocol should be suspended based on the discussion with the DSMC clinician. This is the major function of the email notification. Enter whether the protocol should be suspended in the Event Narrative Field.
5. Follow up/update the clinical member(s) of DSMC regarding any new developments or information obtained during the course of the SAE investigation and reporting process.

Elements needed to complete the SAE form in the Subject Console in WISER (see Screen Shot 3):

1. Event Date
2. Reported Date
3. Reported by
4. If Grade 5, enter Death Date
5. If Grade 5, enter Death occurred: within 30 days
6. Event Narrative: Brief description (include brief clinical history relevant to this event, including therapies believed related to event). Begin narrative with the DSMC clinician who was notified and Date/Time notified. In addition, state attribution by DSMC clinician as either "Unrelated", "Unlikely", "Possibly", "Probably", or "Definitely". Always include the following here:
    i. DSMC clinician name, date/time contacted and comments
    ii. Date of last dose before the event
    iii. Is suspension of the protocol needed? Y/N
7. Treating Physician comments
8. PI comments, if available
9. Protocol Attribution after discussion with DSMC clinician
10. Outcome (Fatal/Died, Intervention for AE Continues, Migrated AE, Not Recovered/Not Resolved, Recovered/Resolved with Sequelae, Recovered/Resolved without Sequelae, Recovering and Resolving)
11. Consent form Change Required? Y/N
12. SAE Classification ***This is required in order for the email notification to be sent***
13. Adverse Event Details – Enter all details for each AE associated with the SAE.
    a. Course start date
    b. Category
    c. AE Detail
    d. Comments
    e. Grade/Severity
    f. Unexpected Y/N
    g. DLT Y/N
    h. Attributions
    i. Action
    j. Therapy
    k. Click ADD to attach the AE Detail to the SAE.
14. Enter Date Notified DSMC -- ***This is required for the email notification to be sent***
15. Click Submit. The auto-generated notification email will disseminate within 5 minutes. If you do not receive an email within 5 minutes, check that you have entered the "Date Notified DSMC" and

the "SAE Classification". If these have been entered and the email still has not been received, take a screen shot of the SAE in WISER and immediately email it out to all of the DSMC members listed in this SOP. In the subject line, indicate that this is a manual transmission of the SAE in lieu of the auto-generated email. It is required that a notification goes to the DSMC members immediately so that their assessment can be obtained within the 24 hour period requirement. Contact the Cancer Center Programmer/Analyst to alert that there is an issue with the auto-generated email.

The Clinical Members of DSMC to Notify by Phone or Page:

Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
Lesser	Hughes	Goodman	Reed	Porosnicu	Seegars	Lesser
Hughes	Goodman	Reed	Porosnicu	Seegars	Lesser	Hughes
Goodman	Reed	Porosnicu	Seegars	Lesser	Hughes	Goodman
Reed	Porosnicu	Seegars	Lesser	Hughes	Goodman	Reed
Porosnicu	Seegars	Lesser	Hughes	Goodman	Reed	Porosnicu
Seegars	Lesser	Hughes	Goodman	Reed	Porosnicu	Seegars

Glenn Lesser, MD – Hematology Oncology
Mercedes Porosnicu, MD-- Hematology Oncology
Ryan Hughes, MD – Radiation Oncology
Michael Goodman, MD -- Hematology Oncology
Daniel Reed, MD -- Hematology Oncology
Mary Beth Seegars, MD -- Hematology Oncology

Definition of Unavailable:

As a general guideline if the first clinician that is contacted does not respond to the phone call or page within 30 minutes, then initiate contact with the next DSMC clinician listed in the table above on the particular day the SAE is being reported. Allow up to 30 minutes for the new DSMC clinician to respond to a phone call or page before contacting the next member in the table. These times (30 minutes) are a general guideline. Best judgment as a clinical research professional should be used giving considerations of the time of day, severity of the SAE, and other circumstances as to when it is appropriate to contact backup clinicians. If the event occurs near the end of day, then leave messages (voice or email) as appropriate and proceed with submitting the DSMC notification form. It is important to take reasonable steps and to document that some type of contact has been initiated to one or more of the clinical members of DSMC.

DSMC CLINICAN RESPONSIBILITY:

It is the responsibility of the DSMC clinician to review all reported events, evaluate the events as they are reported; and communicate a response to the Investigator, event reporter and the members of DSMC. The review will include but not be limited to the information reported; there may be times when additional information is needed in order for an assessment to be made and further communication directly with the investigator may be warranted. DSMC reserves the right to disagree with the Investigator's assessment. If DSMC does not agree with the Investigator, DSMC reserves the right to suspend the trial pending further investigation. If there is any immediate danger or harm that could be present for a future patient based on the information provided in the DSMC report then an immediate

suspension of enrollment shouldbe considered.

AMENDMENTS TO PREVIOUS REPORTS

If all pertinent information is unavailable with the initial submission, once the additional information is available **do not submit a new report**. Rather, go to the original email that was sent to the DSMC and using that email "reply to all". Entitle this new email "**Amendment** for (list date of event and patient ID)" this will avoid duplications of the same event. List the additional information being reported. This information needs to be entered into WISER as well. To do this, go to the Subject console and click SAEs on the left column. Click on the appropriate SAE number that needs updating. Then click Update. This will allow additional information to be added.

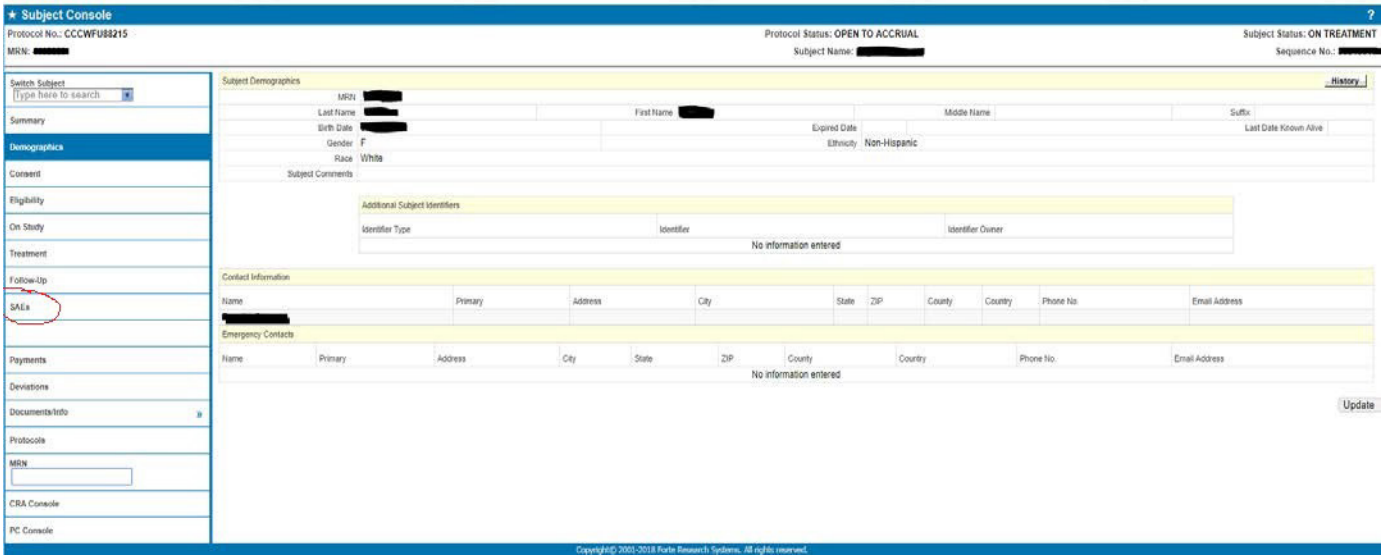
Acronyms

AE – Adverse Event
DSMC-Data and Safety Monitoring Committee
SAE-Serious Adverse Event
WFBCCC – Wake Forest Baptist Comprehensive Cancer Center
NCI-National Cancer Institute
WISER –Wake Integrated Solution for Enterprise Research

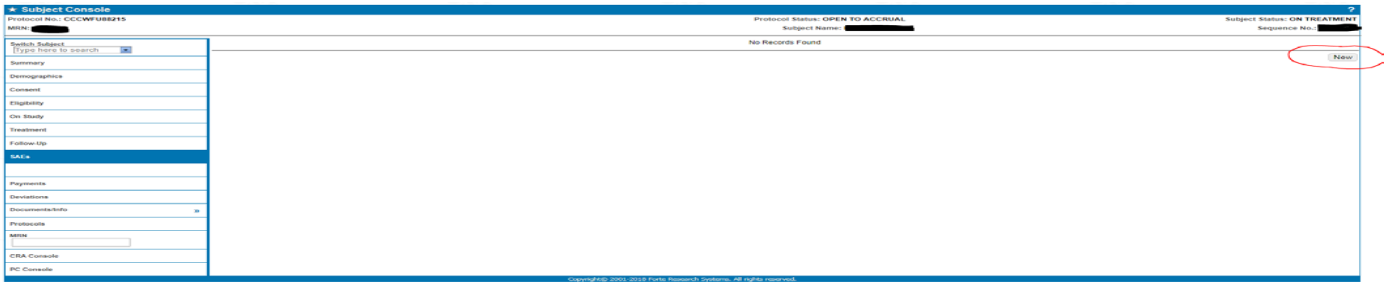
Screen Shots:

The following screen shots come from the SAE Console within the Subject Console in WISER.

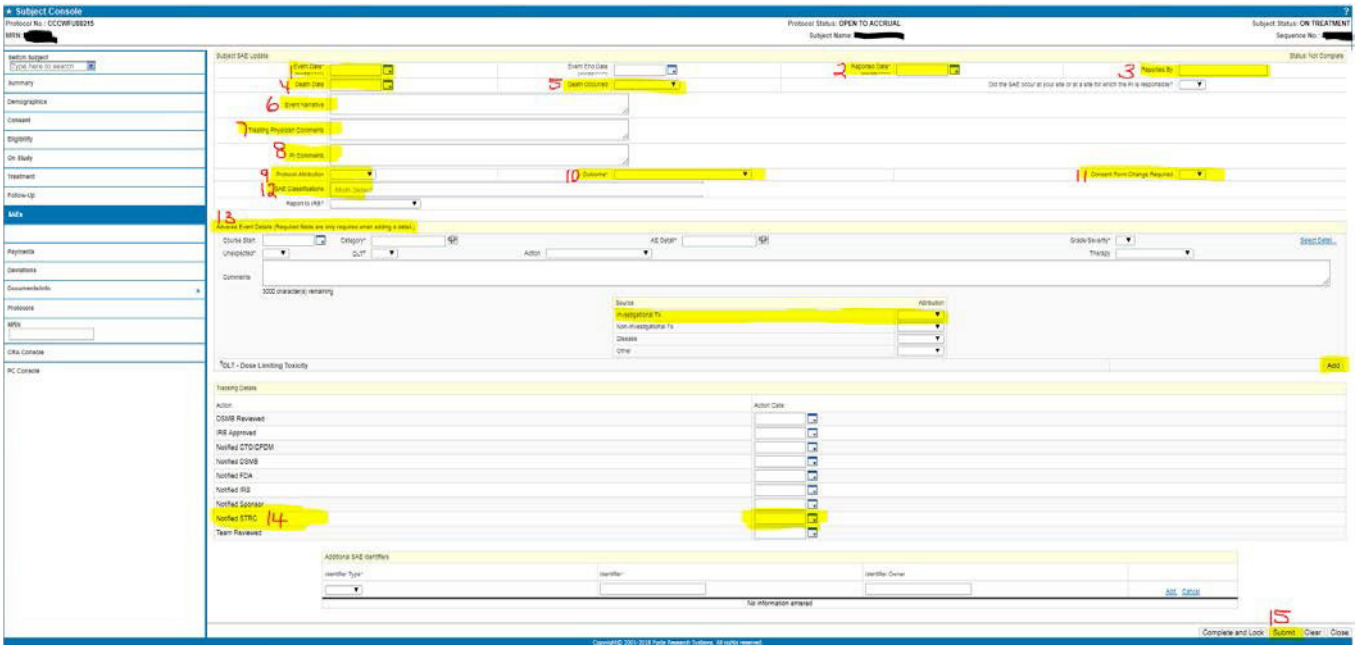
Screen Shot 1:



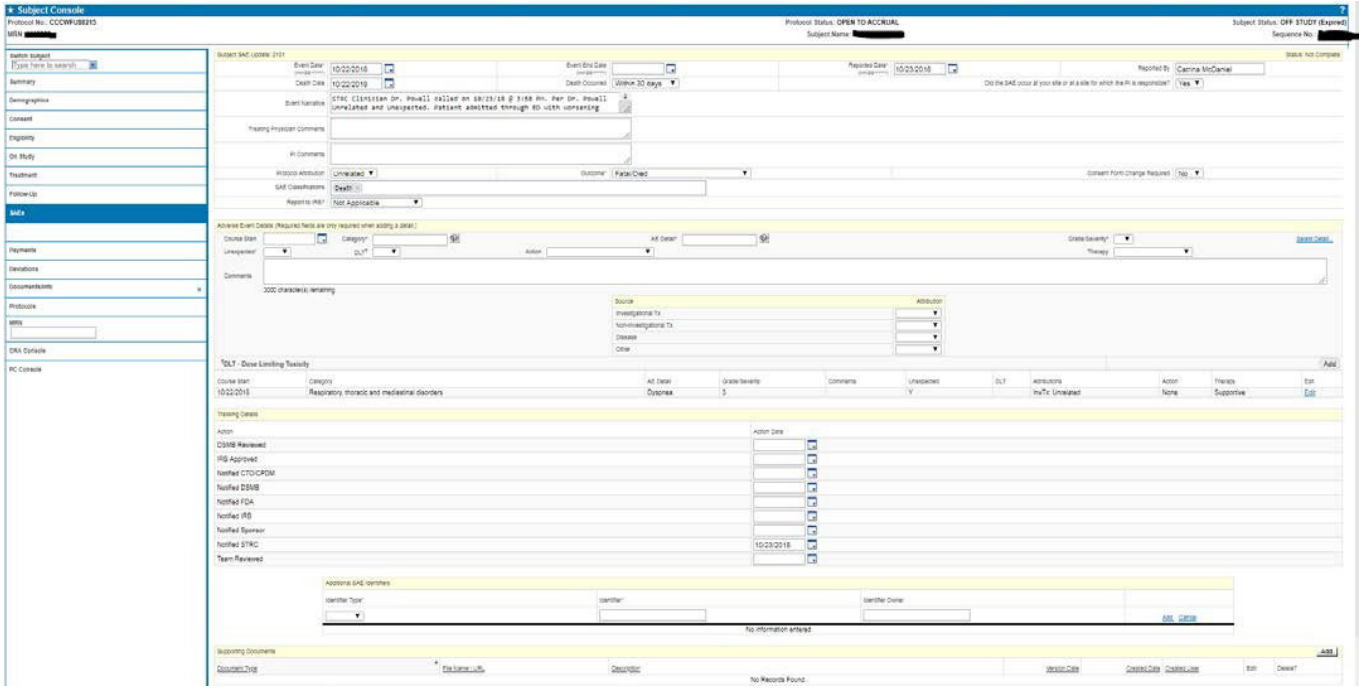
Screen Shot 2:



Screen Shot 3:



Screen Shot 4:



Cultural and Linguistic Adaptation of a Telephone-Based Intervention to Treat Depression and Anxiety in Hispanic Cancer Survivors

Wake Forest Baptist Comprehensive Cancer Center

WFBCCC # 01220