COVER PAGE

DCP Protocol #: WF-30917CD

Local Protocol #: WF-30917CD

A STEPPED-CARE TELEHEALTH APPROACH TO TREAT DISTRESS IN CANCER SURVIVORS

Consortium Name: **Wake Forest NCORP Research Base**
Name of Consortium Multi-Principal Investigator **Glenn Lesser, MD**
Department of Internal Medicine
Section on Hematology and Oncology
Wake Forest School of Medicine
Medical Center Boulevard
Winston-Salem, NC 27157
Telephone: (336) 716-0891
Fax: (336) 716-6275
E-mail address: glesser@wakehealth.edu

Consortium Name: **Wake Forest NCORP Research Base**
Name of Consortium Multi-Principal Investigator **Kathryn Weaver, PhD, MPH**
Associate Professor of Public Health Sciences
Department of Social Sciences & Health Policy
Medical Center Boulevard
Winston-Salem, NC 27157
Telephone: (336)713-5062
Fax: (336) 716-7554
E-mail address: keweaver@wakehealth.edu

Organization Name: **Wake Forest School of Medicine**
Protocol Principal Investigator: **Suzanne C. Danhauer, PhD**
Department of Social Sciences & Health Policy
Division of Public Health Sciences
Medical Center Boulevard
Winston-Salem, NC 27157
Telephone: (336) 716-7402
Fax: (336) 716-7554
E-mail address: danhauer@wakehealth.edu

Organization Name: **Wake Forest School of Medicine**
Protocol Principal Investigator: **Gretchen A. Brenes, PhD**
Department of Internal Medicine, Section on Gerontology and Geriatric Medicine
Medical Center Boulevard
Winston-Salem, NC 27157
Telephone: (336) 716-1103
Fax: (336) 716-6830
E-mail address: gbrenes@wakehealth.edu

Organization: **Wake Forest School of Medicine**
Investigator: **Kathryn Weaver, PhD**
Department of Social Sciences & Health Policy
Division of Public Health Sciences
Medical Center Boulevard
Winston-Salem, NC 27157
Telephone: (336) 716-0891
Fax: (336) 713-6476
E-mail address: keweaver@wakehealth.edu

Organization: **Wake Forest School of Medicine**
Investigator/Protocol Statistician: **Janet A. Tooze, PhD**
Department of Biostatistical Sciences
Division of Public Health Sciences
Medical Center Boulevard
Winston-Salem, NC 27157
Telephone: (336) 713-3833
Fax: (336) 716-6427
E-mail address: jtooze@wakehealth.edu

Organization: **Wake Forest School of Medicine**
Investigator: **Rakhee Vaidya, MD**
Department of Hematology and Oncology
Division of Public Health Sciences
Medical Center Boulevard
Winston-Salem, NC 27157
Telephone (336) 713-3833
Fax: (336) 716-2774
E-mail address: ravaidya@wakehealth.edu

Organization: **University of Alabama**
Investigator **Maria Pisu, PhD**
Division of Preventative Medicine
Medical Towers 636
1717 11th Avenue South
Birmingham, Alabama 35205
Telephone: (205) 975-7366
Fax: (205) 934-7959
E-mail address: mpisu@uab.edu

Organization: **Wake Forest School of Medicine**
Wake Forest RB Statistician: **Emily V. Dressler, PhD**
Division of Public Health Sciences
Department of Biostatistics and Data Science
Medical Center Boulevard
Winston-Salem, NC 27157
Telephone: (336) 716-0917
Fax: (336) 716-6427
E-mail address: edressle@wakehealth.edu

Grant #: 1 R21 CA198237-01A1

Protocol Amendment #: 5
Protocol Version Date: 12/09/2020

Protocol History:

Initial	Version 12/21/2017	Not Activated
Amendment 1	Version 03/16/2018	Activated 06/18/2018
Amendment 2	Version 06/22/2018	Activated 08/10/2018
Amendment 3	Version 09/19/2018	Activated 04/29/2019
Amendment 4	Version 11/20/2019	Activated 04/27/2020

Participating Organizations

NCORP Limited Participation: Wake Forest NCORP Affiliates and Sub-affiliates

<table>
<tr><td colspan="3">CONTACT INFORMATION</td></tr>
<tr><td>For regulatory requirements:</td><td>For patient enrollments:</td><td>For data submission:</td></tr>
<tr><td>Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal.
Regulatory Submission Portal: (Sign in at www.ctsu.org, and select the Regulatory → Regulatory Submission.)

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support.

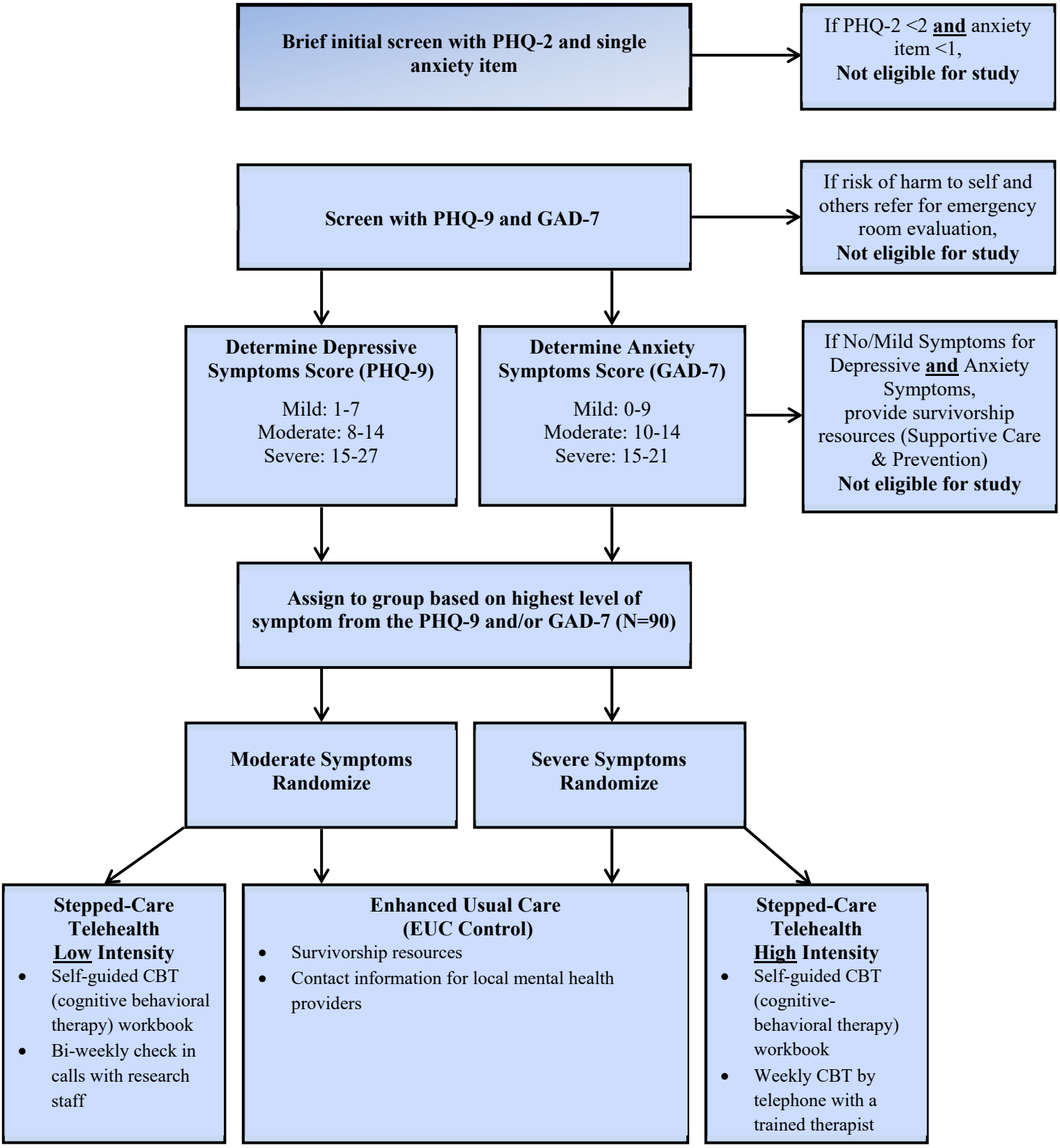
Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.</td><td>Please refer to the patient enrollment section of the protocol for detailed instructions.</td><td>Data will be submitted to the WF NCORP Research Base.

Address:
WF NCORP Research Base
Wake Forest Baptist Medical Center
Building 525@Vine, 4th floor
Medical Center Boulevard
Winston-Salem, NC 27157

Fax: (336) 713-6476
Email: NCORP@wakehealth.edu

Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.</td></tr>
<tr><td colspan="3">The most current version of the study protocol and all supporting documents must be downloaded from the protocol-specific page of the CTSU member's website https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password.</td></tr>
<tr><td colspan="3">For clinical questions (i.e. patient eligibility or treatment-related) contact the Site Coordinator at Wake Forest NCORP Research Base at NCORP@wakehealth.edu.</td></tr>
<tr><td colspan="3">For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail:
CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.</td></tr>
</table>

SCHEMA


Brief initial screen with PHQ-2 and single anxiety item
If PHQ-2 <2 and anxiety item <1, Not eligible for study
Screen with PHQ-9 and GAD-7
If risk of harm to self and others refer for emergency room evaluation, Not eligible for study
Determine Depressive Symptoms Score (PHQ-9)
Mild: 1-7
Moderate: 8-14
Severe: 15-27
Determine Anxiety Symptoms Score (GAD-7)
Mild: 0-9
Moderate: 10-14
Severe: 15-21
If No/Mild Symptoms for Depressive and Anxiety Symptoms, provide survivorship resources (Supportive Care & Prevention) Not eligible for study
Assign to group based on highest level of symptom from the PHQ-9 and/or GAD-7 (N=90)
Moderate Symptoms Randomize
Severe Symptoms Randomize
Stepped-Care Telehealth Low Intensity
Self-guided CBT (cognitive behavioral therapy) workbook
Bi-weekly check in calls with research staff
Enhanced Usual Care (EUC Control)
Survivorship resources
Contact information for local mental health providers
Stepped-Care Telehealth High Intensity
Self-guided CBT (cognitive-behavioral therapy) workbook
Weekly CBT by telephone with a trained therapist

STUDY SUMMARY

Endpoints: Feasibility (accrual, retention, adherence), anxiety, and depressive symptoms, cost.

Stratification Participants will be stratified by baseline score ≥15 on the GAD-7 and/or on the PHQ-9, indicating severe anxiety or depressive symptoms, and by whether they qualified for the study by the GAD-7, PHQ-9, or both.

Study Sample: 90 participants

Study Duration: 13 - 15 weeks

Brief Eligibility Criteria:

- Age ≥18 years
- Score ≥10 on the GAD-7 and/or a score ≥8 on the PHQ-9, indicating clinically significant anxiety or depressive symptoms, respectively.
- Past history of treated Stage I, II, or III (newly diagnosed or recurrent) of any of the following cancers: breast, colorectal, prostate, gynecologic (only uterine and cervical) and any stage lymphoma (Hodgkin's or non-Hodgkin's).
- 6-60 months post-treatment completion (surgery, chemotherapy, and/or radiation therapy) for cancer. Time frame applies to most recent completion of treatment if participant had a cancer recurrence. It is acceptable to be on hormonal therapies.
- Participant resides in California, Georgia, Illinois, Kansas, Michigan, Minnesota, Missouri, New Mexico, North Carolina, North Dakota, South Carolina, Virginia, Tennessee, or Wisconsin.
- Study trained therapist in state where participant resides.
- Must be able to speak and understand English.
- Must have access to a telephone.

TABLE OF CONTENTS

Appendices:

1. OBJECTIVES

1.1 Primary Objectives

1.1.1. To determine feasibility (recruitment, accrual, retention, adherence) of a RCT of a stepped-care telehealth mental health intervention (tailored to symptom level) versus enhanced usual care in 90 post-treatment cancer survivors with moderate or severe levels of emotional distress (anxiety and/or depressive symptoms).

1.2 Secondary Objectives

1.2.1. To obtain preliminary data on the efficacy and variability of a stepped-care telehealth mental health intervention (tailored to symptom level) versus enhanced usual care for reducing emotional distress (anxiety and/or depressive symptoms) in 90 post-treatment cancer survivors.

1.2.2. To obtain preliminary data on the efficacy and variability of a stepped-care telehealth mental health intervention (tailored to symptom level) versus enhanced usual care for secondary outcomes (sleep disturbance, fatigue, fear of recurrence, cancer-related distress, and QOL) in 90 post-treatment cancer survivors.

1.2.3. To determine costs associated with both stepped-care telehealth and enhanced usual care interventions from the perspective of a healthcare provider. We will determine costs of intervention implementation and health care utilization in all arms over the course of the interventions.

1.3 Exploratory Objectives

1.3.1. To examine potential differential effects of the intervention on anxiety, depression, sleep disturbance, fatigue, fear of recurrence, and QOL, by gender, age, race/ethnicity, rural v. urban status, stratification arm (moderate, severe), and psychotropic medication use at baseline.

1.3.2 To examine mediating effects of expectancy ratings of the intervention on anxiety and depression.

2. BACKGROUND

2.1 Distress in Cancer Survivors

Psychological concerns are among the most commonly reported unmet needs among post-treatment cancer survivors.[1] Psychosocial distress, including anxiety and depressive symptoms, is also common.[2–14] Up to 54% of post-treatment cancer survivors report clinically significant distress,[4,15] which is associated with multiple adverse outcomes, including decreased quality of life (QOL),[10,16,17] functional limitations,[18,19] poor sleep,[20,21] increased pain,[14] and – particularly for those with elevated depressive symptoms – increased mortality.[22,23] The Institute of Medicine has emphasized post-treatment survivorship as a "distinct phase of cancer care," with a need for ensuring delivery of appropriate care for cancer survivors.[24] The need for interventions to reduce psychosocial morbidity in post-treatment cancer survivors is critical.[6,25] Psychosocial interventions for post-treatment cancer survivors may improve mental and physical health, potentially offsetting increased health care costs among distressed cancer survivors.[26]

Mental health issues are more prevalent among the 2.8 million US cancer survivors living in rural (versusnon-rural) areas,[27] further illustrating how the "burden of cancer is magnified among the US rural population."[28] Rural cancer survivors report more mental health concerns than non-rural cancer

survivors,[29] yet psychosocial care for cancer survivors is scarce in many rural areas.[15,24,28,30] Almost 21% of U.S. cancer survivors reside in rural areas,[25,27] and over half of rural counties have no mental health professionals.[31] Recent studies found poorer accessibility to mental health professionals[29] and higher levels of unmet needs[3] in rural cancer survivors. Interventions that are accessible to post-treatment cancer survivors experiencing significant distress may reduce this cancer heath disparity.

2.2 Rationale

Noting the need for evidence-based cancer survivorship care, the American Society of Clinical Oncology (ASCO) published guidelines for screening, assessment, and care of psychosocial distress (anxiety, depression) in adults with cancer.[6] These guidelines recommend screening all adults with cancer for distress and treating those with moderate or severe symptoms using a stepped-care approach tailored to distress severity. While these guidelines apply to survivors with all cancer types across the cancer treatment and survivorship continuum, we have chosen to focus on survivors with non-metastatic breast, colorectal, prostate, uterine, and cervical cancers , as well as those with any stage lymphoma (Hodgkin's or non-Hodgkin's). Further, we have focused on the post-treatment survivorship period 6 months-5 years post-treatment because distress may be more likely to be assessed and addressed after treatment completion. A significant minority of post-treatment survivors is at risk for anxiety and depression symptoms during the five years following the end of treatment and accessible interventions are needed to treat them.

The purpose of this study is to test a method of implementing this stepped-care approach in community oncology practices caring for cancer survivors, using self-directed and stepped-care telehealth approaches based on cognitive-behavioral theory. Our approach is based on a previous trial of telephone-based cognitive behavioral therapy for rural older adults with Generalized Anxiety Disorder (NIMH 1R01MH083664: The Tranquil Moments Study; PI: Brenes), which has demonstrated high acceptability and efficacy for reducing anxiety, worry, and depressive symptoms in a rural geriatric population.[32] This protocol adapts the methods of the previous trial to bring psychosocial care to underserved cancer survivors, many of whom have minimal or no access to mental health providers. Cancer survivors will be recruited through multiple NCI Community Oncology Research Program (NCORP) sites through the NCI-funded Wake Forest NCORP Research Base (WF NCORP RB).

We will obtain data on feasibility, outcome variability, and efficacy for designing a subsequent fully powered randomized controlled trial (RCT) assessing the effects of the intervention on distress in cancer survivors. In the planned larger study, we anticipate that this intervention will: (a) reduce treatment barriers for post-treatment cancer survivors; (b) enhance availability of psychosocial treatment (through use of telephone sessions and a workbook); and (c) result in reductions in anxiety and depressive symptoms in cancer survivors.

3. SUMMARY OF STUDY PLAN

This study compares a stepped-care telehealth intervention (tailored to level of symptomatology and designed to reduce anxiety and depressive symptoms) with enhanced usual care (EUC). Participants with no/mild symptoms will be provided survivorship resources and will not be included in the trial.

A total of 90 participants will be randomized. Study screening will be completed by a Research Nurse or an appropriate designated research staff member at each NCORP component. Assuming an accrual rate of approximately 8-9 randomized participants per month, we expect study recruitment to be complete within 11 months.

Referred participants will waive documentation of informed consent to complete the PHQ-2 and single anxiety question. If a participant scores ≥ 2 on the PHQ-2 or ≥ 1 on the anxiety question, he/she will be invited to complete the full screening assessment to determine study eligibility. The participant will complete the Abbreviated Verbal Consent at this point. We are asking to waive the following elements of

consent for this second step of screening: disclosure of appropriate alternatives, statements regarding who may access the participant's medical record for verification, and compensation for injury. If they meet all eligibility criteria and want to participate in the randomized trial, they will provide full informed consent for study participation. Trained research staff members at each NCORP component will obtain full informed consent from all interested and eligible potential participants.

In accordance with ASCO guidelines, participants with no/mild symptoms will be provided with written survivorship resources (a letter that contains a link to the National Cancer Institute booklet "Facing Forward: Life after Cancer Treatment") and will not be randomized (Appendix 20). Participants with either moderate or severe distress (anxiety or depressive symptoms) will be randomized into stepped-care telehealth (tailored to level of symptoms) or EUC. For participants with moderate symptoms (PHQ-9: 8-14; GAD-7: 10-14), low-intensity stepped-care telehealth will consist of a self-guided cognitive behavioral therapy (CBT) workbook to reduce anxiety and depressive symptoms and biweekly (every two weeks) check-in calls from research staff at NCORP components. On the biweekly check-in calls, research staff from NCORP components will provide minimal support and will administer the scripted "Telephone Script/Manual for Low-Intensity Group Check-in Call Form." This form assesses changes in symptom severity during the past two weeks. The site staff person is directed to follow Telehealth crisis protocol, refer to Appendix 21, for participants indicating "thoughts of death or suicidal ideation." Site staff should also follow crisis procedures for any other problems identified during administration of the form where follow-up is needed.

For participants with severe symptoms (PHQ-9: 15-27; GAD-7: 15-21), high intensity stepped-care telehealth will consist of a CBT workbook with accompanying psychotherapy by a Master's- or doctoral-level therapist delivered by telephone. Participants randomized to EUC will receive survivorship resources (Appendix 20) and referral information for local mental health providers.

4. PARTICIPANT SELECTION

4.1 Inclusion Criteria

4.1.1. Age ≥18 years

4.1.2. Score ≥10 on the GAD-7 and/or a score ≥8 on the PHQ-9, indicating clinically significant anxiety or depressive symptoms, respectively.

4.1.3. Past history of treated (newly diagnosed or recurrent)[28,29] breast, colorectal, prostate, gynecologic (only uterine and cervical) cancers (Stage I, II, or III) or any stage lymphoma (Hodgkin's or non-Hodgkin's).

4.1.4. 6-60 months post-treatment (surgery, chemotherapy, radiation therapy, and/or maintenance therapies) for cancer. Time frame applies to most recent completion of treatment if participant had a cancer recurrence. It is acceptable to be on hormonal therapies.

4.1.5. Participant resides in California, Georgia, Illinois, Kansas, Michigan, Minnesota, Missouri, New Mexico, North Carolina, North Dakota, South Carolina, Virginia, Tennessee, or Wisconsin.

4.1.6. Study-trained therapist in the state where the participant resides.

4.1.7. Must be able to speak and understand English.

4.1.8. Must have access to a telephone. If a patient does not have access to a phone or has difficulty paying for minutes for a mobile phone, the research team should contact the Wake Forest investigators or site coordinators to arrange for assistance.

4.2 Exclusion Criteria

4.2.1. Current psychotherapy [regular appointment(s) with a psychologist, counselor, or therapist within the last 30 days prior to randomization]

4.2.2. Self-reported active alcohol or substance abuse within the last 30 days

4.2.3. Past history of prostate cancer or non-Hodgkin's lymphoma with only active surveillance (i.e., no surgery, chemotherapy, or radiation therapy)

4.2.4. Progressive cancer (must be considered no evidence of disease or stable)

4.2.6. Self-reported psychotic symptoms in the last 30 days prior to randomization (See item in Appendix 4: "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?")

4.2.7. Active suicidal ideation with plan and intent

4.2.8. Any change in psychotropic medications within the last 30 days (See Appendix 25)

4.2.9. Hearing loss that would preclude participating in telephone sessions (determined by brief hearing assessment administered by research staff at each NCORP component). 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.

4.2.10. 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

4.3 Inclusion of Women and Minorities

Both men and women (as applicable) and members of all races and ethnic groups are eligible for this trial.

	Females	Males	Total
Ethnic			
Hispanic	8	7	15
Not Hispanic	40	35	75
ETHNIC TOTAL	48	42	90

	Females	Males	Total
Racial			
Am Indian	1	0	1
Asian	2	1	3
Native Hawaiian	0	0	0
Black	6	9	15
White	39	32	71
RACIAL TOTAL	48	42	90

4.4 Recruitment and Retention Plan

Participants will be followed for 13 - 15 weeks. After the Week 13 visit (for participants in the intervention group, Week 13 measures should be completed after the intervention is finished and could be Weeks 13 – 15), the participant is no longer followed and data are no longer collected from the participant.

NCORP sites will accrue to this trial through the National Cancer Institute NCORP program. The WF NCORP RB will sponsor and administer this trial. There will be a secure, password protected TELEHEALTH study website for the management of study participants including randomization, schedule of study visits and data entry of forms designated to be entered by site staff. Data reports and documents will also be available.

Potential participants may be recruited via (1) in-clinic screening during medical appointments; (2) identifying survivors through the site cancer registry; (3) screening clinic charts; and (4) participant recruitment flyers (Support Document 5) and recruitment letters (Support Document 4). Local sites should check with their IRBs to determine if a partial HIPAA waiver is required for the review of participant medical records/charts. Survivors will be approached in-person or by telephone by NCORP staff to ascertain interest and initial eligibility. We will track numbers of survivors approached and screened, reasons for nonparticipation, and number randomized. All written materials will be at an 8th grade reading level.

We expect to recruit minority participants through several strategies. (1) We will request review of our protocol and recruitment materials from the Wake Forest Baptist Comprehensive Cancer Center Cancer Office of Cancer Health Equity (for whom Dr. Weaver serves as an Assistant Director) and the Wake Forest NCORP Research Base (WF NCORP RB) for suggestions to enhance the appeal of our study to minority participants. (2) We will inform all Minority-Underserved NCORPs affiliated with the WF NCORP RB in targeted states about the study and seek their feedback on how to enhance minority recruitment. Working with Dr. Glenn Lesser, PI of the WF NCORP RB, we will additionally reach out to Minority-based NCORPs not currently affiliated with Wake Forest, but with components/sub-components in targeted states and encourage them to participate in this study. (3) We will emphasize the importance of robust minority accrual at our study kickoff meetings and provide specific education and discussion about strategies to overcome barriers that underserved patients may experience to study participation. (4) We will monitor minority recruitment rates at our monthly WF NCORP RB executive committee meetings and provide feedback to the NCORP sites via bimonthly study teleconference calls. Specifically, we will monitor the minority recruitment rate in conjunction with available data about the population of eligible patients at the site to identify sites that are potentially under-performing with regard to minority accrual. Sites with strong minority recruitment will be asked to share their experiences with other sites during these calls.

Several elements of this trial were designed with retention in mind. First, the follow-up period is brief, with total study enrollment lasting only 13 – 15 weeks. Second, the stepped-care telehealth group will receive weekly or biweekly (every two weeks) calls from research staff at NCORP components or therapists. We will send thank-you letters to the enhanced usual care group following their assessments at baseline and 7 weeks (Support document 6). Finally, if a participant does not have a telephone or is unable to purchase minutes for their mobile phone to participate in the study intervention or assessments, the research team should contact the Wake Forest investigators or site coordinators to arrange for assistance.

5. INTERVENTION PARAMETERS (RETENTION, ADHERENCE, TREATMENT FIDELITY)

5.1 Study retention

Study retention will be estimated by the proportion of participants who complete the Week 7 and 13 visits.

5.2 Adherence

Adherence will be recorded as the percentage of therapy sessions (for the high-intensity intervention group) or check-in calls (for the low-intensity intervention group) each participant completes.

5.3 Treatment Fidelity

For the purposes of the study, therapists (who may or may not be employees at NCORP component sites) are considered to be research therapists and will contract (or subcontract) with the study to directly provide services for the research grant. As part of the contract, research therapists will be required to meet quality metrics including the audiotaping of psychotherapy sessions to ensure treatment fidelity. All therapy sessions will be audiotaped, and 8% of psychotherapy sessions (1 session per randomized participant) will be randomly selected for review (not live) by Dr. Brenes using a measure of therapist adherence (Appendix 18) and competence developed and used by Stanley and colleagues (Stanley et al., 1996; Stanley et al., 2003). This measure assesses both the competence and adherence of the therapist in the delivery of the specific skills of the intervention (e.g., progressive muscle relaxation, problem solving, etc.) as well as an overall rating of therapist competence and adherence. Data suggest high internal consistency (alpha = .91-.94) and greater variability in ratings attributed to clinicians (29%) than raters (9%), suggesting good reliability of the instruments (personal communication, Dr. Melinda Stanley; see Appendix 18 for a copy of this measure.)

Local site staff that are part of the research team and are responsible for making check-in calls with study participants will be audio-taped for adherence to study protocol and competence. All check-in calls will be audiotaped and 16% of calls (1 session per participant) will be randomly selected for review (not live) by Dr. Danhauer using a measure of adherence and competence developed for this study (see Appendix 19 for a copy of this measure.) Dr. Danhauer will meet via telephone with the research staff whose ratings indicate difficulties in intervention delivery.

Therapists (CBT)/research staff (check-in calls) who do not demonstrate competency (competency score < 6) will receive additional training until competency is demonstrated. Dr. Brenes will meet with therapists on a regular basis to discuss cases, review therapist adherence and competence ratings, and answer questions regarding protocol administration. Any areas of nonadherence will be reviewed, and the therapist will review any difficulties in intervention delivery.

The primary purpose of the data collected from the audiotaped therapy sessions and check-in calls is to identify research personnel who are not implementing the protocol/intervention with fidelity and to provide these personnel with additional supervision and/or training to improve protocol adherence. This is a common approach used in clinical trials of psychotherapy and behavioral interventions. The study will not use aggregate data from the audiotaped sessions/calls as a feasibility/adoption metric.

Study therapists will meet regularly with Drs. Brenes or Danhauer for ongoing discussion of cases and study supervision.

5.4 Management of Study Risk

The following procedures are in place to protect against possible risks:

Participants who are at high risk for adverse outcomes (e.g., active suicidal ideation with plan and intent, current psychosis) will be excluded from the study. Participants who do not meet study inclusion criteria will be provided with alternative referrals. If any participant shows evidence of the need for immediate treatment (e.g., active psychosis, suicidal intent) at any time during the consent, assessment, and treatment periods, the participant will be referred for immediate psychiatric assistance (as specified in the Crisis Protocol, Appendix 21), and one of the co-PIs will be notified.

The only risk of this study is that some individuals may find discussing their problems with others to be uncomfortable, embarrassing, and/or stressful. This is expected to be temporary. All study staff will be trained to deal with these situations, and every effort will be made to address each participant's concerns or problems in the most supportive, empathic, and therapeutic manner.

5.5. Crisis Protocol

If any participant 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] from baseline) or the participant expressed suicidal ideation on the PHQ-9 (Question 9 score of >2), the computer software system will automatically generate an e-mail to the co-PIs and the Wake Forest School of Medicine Project Manager. The co-PIs or Project Manager will follow up with staff (either the therapists for participants in the high-intensity stepped-care telehealth or site personnel for participants in the low-intensity stepped-care telehealth or usual care arms) to enact 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 psychiatric 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, based on our prior studies, no participants randomized into the study became imminently suicidal. All study staff (therapists, site 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, sites will have 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 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 by mail with a request that the participant contact the therapist regarding interest in continuing the study sessions.

5.5.1. Emergency Contacts

As an additional safety precaution and part of the screening, participants will provide the names of two emergency contacts and their phone numbers. Study staff will contact the emergency contacts if needed during the administration of the Crisis Protocol or in any other emergency. If the Crisis Protocol is activated during a study session or contact and the participant misses the next scheduled session, then the therapist will call the emergency contacts immediately.

6. REGISTRATION

6.1 Investigator and Research Associate Registration with CTEP

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) https://ctepcore.nci.nih.gov/rcr.

RCR utilizes five person registration types.

- IVR — MD, DO, or international equivalent;
- NPIVR — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- AP — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System [RUMS], OPEN, Rave, acting as a primary site contact, or with consenting privileges;
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✓	✓			
Financial Disclosure Form	✓	✓	✓		
NCI Biosketch (education, training, employment, license, and certification)	✓	✓	✓		
GCP training	✓	✓	✓		
Agent Shipment Form (if applicable)	✓				
CV (optional)	✓	✓	✓		

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster
- Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol Principal Investigator (PI) on the IRB approval; and
- Assign the Clinical Investigator (CI) role of the Delegation of Tasks Log (DTL)

In addition, all investigators act as the Site-Protocol PI (investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, or as the CI on the DTL must be rostered at the enrolling site with a participating organization.

Additional information is located on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the **RCR Help Desk** by email at RCRHelpDesk@nih.gov.

6.2 Cancer Trials Support Unit Registration Procedures

Protocol documents are found on the CTSU website, but additional supplemental documents may be available on the Wake Forest NCORP Research Base website (https://wakencorp.phs.wakehealth.edu/dspLogin.cfm).

This study is supported by the NCI CTSU.

IRB Approval:

For CTEP and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB). In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet for Local Context (SSW) to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by emailing the email address above or calling 1-888-651-CTSU (2878).

In addition, the Site-Protocol Principal Investigator (PI) (i.e. the investigator on the IRB/REB approval) must meet the following criteria in order for the processing of the IRB/REB approval record to be completed:

- Holds an Active CTEP status;
- Rostered at the site on the IRB/REB approval (applies to US and Canadian sites only) and on at least one participating roster;
- If using NCI CIRB, rostered on the NCI CIRB Signatory record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements

Additional requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;

- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO); and
- Compliance with all protocol-specific requirements (PSRs).

6.3 Protocol Specific Requirements for WF-30917CD Site Registration:

- NCI CIRB approval – all participating sites must use the NCI CIRB as their IRB of record for WF-30917CD.
- Confirmed study-trained therapist for the state in which the site is located who has completed protocol specific training.
- Site Open to Enrollment (SOTE) letter from WF NCORP RB, which is provided to the site once all start-up activities have been completed.

Practice Level Data Collection Form – The enrolling affiliate/sub affiliate will complete the NCORP Practice Level Data Collection Form and submit it to the CTSU Regulatory Office using the Regulatory Submission Portal located in the Regulatory section of the CTSU website. The form will collect various attributes about the enrolling affiliate/sub affiliate. All of the questions on the form must be complete and the distribution for the analytic cases question must equal 100%. (See form for directions.) The form must be received and complete for site registration approval in RSS. The Practice Level Data Collection Form requirement is submitted once for participation on all NCORP Cancer Care Delivery (CCDR) trials, but will expire two years after it is received. NCORP sites will need to resubmit the Practice Level Data Form to the CTSU in order to continue to enroll to CCDR trials.

6.4 Submitting Regulatory Documents:

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal on the CTSU website.

To access the Regulatory Submission Portal log in to the CTSU members' website, go to the Regulatory section and select Regulatory Submission.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

6.5 Checking Your Site's Registration Status:

Site registration status may be verified on the CTSU member's website.

- Click on *Regulatory* at the top of the screen;
- Click on *Site Registration;* and
- Enter the sites 5-character CTEP Institution Code and click on Go.
    - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type

Note: The status shown only reflects institutional compliance with site registration requirements as outlined above. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

7. CLINICAL EVALUATIONS AND PROCEDURES

7.1 Intervention Description

Participants with moderate anxiety and depressive symptoms will be randomized to either the low-intensity stepped-care telehealth or the EUC control. Participants with severe symptoms will be randomized to either the high-intensity stepped-care telehealth intervention or the EUC control. Therapists participating in the trial must meet the following requirements: a Master's or doctoral degree in counseling, marriage and family therapy, psychology, or social work; licensed as an independent mental health provider in California, Georgia, Illinois, Kansas, Michigan, Minnesota, Missouri, New Mexico, North Carolina, North Dakota, South Carolina, Virginia, Tennessee, or Wisconsin; and experience with cognitive-behavioral therapy. Experience working with oncology patients/survivors is preferred. Therapists will attend a 1.5-day training that will cover information on study design, anxiety and depression in cancer survivors, principles of cognitive-behavioral therapy, delivery of the intervention, and use of the web-based data-entry system. NCORP sites and/or components may nominate therapists for participation, but are not required to identify a therapist to participate. The Wake Forest study team will identify a participating therapist for each state.

Low Intensity Stepped-care Telehealth: The low-intensity stepped-care telehealth group will consist of a self-guided CBT workbook (15 minutes daily to read and complete exercises/homework) and biweekly (every two weeks) check-in calls (5-10 minutes) from an NCORP component research staff person to assess changes in symptom severity/immediate need for psychiatric treatment and provide minimal support. Check-in calls are expected to be completed within +/- 2 days of the window specified in the Telehealth website; however, check-in calls up to +/- 1 week of the window are permitted.

Consistent the ASCO guidelines,[37] the Wake Forest NCORP Research Base staff will mail a professionally-prepared and IRB-approved CBT workbook to participants that focuses on different cognitive-behavioral techniques for managing anxiety, depression, and distress. CBT teaches people to monitor depressive and anxiety-producing thoughts, modify these thoughts, and modify behaviors that reinforce depression and anxiety. 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.

All participants receive 10 identical chapters. 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] These participants will also receive biweekly (every two weeks) check-in calls from a research staff person at NCORP components to provide support and assess symptom severity changes (Appendix 14). Participants with increased symptoms as indicated by 1 standard deviation increase and a total score of ≥15 on either the PHQ-9 or GAD-7 at Week 7 will be moved to the high-intensity treatment or referred for more intensive psychiatric treatment (per the Crisis Protocol, see Appendix 21). If participants are moved from the low intensity to high intensity treatment, the Participant Status Change Form should be completed (Appendix 23). Analysis will proceed as intent-to-treat with their initial stepped-care telehealth level; we do not anticipate that many people will change from moderate to severe during the study.

High Intensity Stepped-care Telehealth: The high-intensity stepped-care telehealth group will consist of the CBT workbook (15 minutes daily to complete exercises/homework), plus psychotherapy delivered by telephone with a licensed therapist (45 minute sessions weekly). If participant is randomized to the High

Intensity Arm, the therapist will make at least one attempt to schedule the participant's first therapy session within 2 weeks of the date of notification via email.

Consistent with the ASCO guidelines,[37] the Wake Forest NCORP Research Base staff will mail a professionally prepared and IRB approved CBT workbook to participants and participants will have 12 weekly therapy sessions with the study therapist. The study therapist will be a licensed mental health provider (e.g., licensed clinical social worker, marriage and family therapist, licensed professional counselor, psychologist). Onsite or phone training is provided for all participating therapists. Training will include the use of the workbook, formal didactic presentations, readings, and role-plays. All study therapists will receive regular (at least monthly) study supervision from Dr. Brenes. There will be at least one trained therapist for each state in the U.S. that has any participating sites. Each week, the participant will receive one 45-minute telephone session and one workbook chapter. The sessions will supplement the participant's understanding of anxiety, depression, and distress management techniques and include a review of the daily workbook exercises to assure understanding and maximize application in daily life.

Enhanced Usual Care. At the time of randomization, EUC participants will receive: (1) information about referrals/resources (Sample Resource Sheet) in their local area, including support groups and mental health providers (Appendix 20 and Support Document 9); (2) information about written self-help resources (several readily available published workbooks) for anxiety and depressive symptoms; and (3) a copy of the National Cancer Institute publication entitled "Facing Forward: Life after Cancer Treatment." This publication can be viewed at the following web link: **https://www.cancer.gov/publications/patient-education/life-after-treatment.pdf.** Site staff should contact the NCORP Research Base site coordinator who will ship a copy of the booklet to each EUC participant within two weeks of randomization. It addresses the topics of follow up medical care, physical changes, body changes and intimacy, feelings, and social and work relationships. Upon completion of the Week 13 post-intervention assessment battery, the Wake Forest NCORP Research Base staff will send a black and white 2-sided copy of the CBT workbook to participants in EUC (same workbook provided to participants in the low-intensity and high-intensity intervention groups). In addition, the EUC randomization script can be used to help explain EUC to participants who are randomized to the EUC condition.

7.2. Schedule of Events

NCORP site or component site staff is responsible for printing and mailing all study assessments and forms to be completed by the participant if forms are not completed by participants at the site. A self-addressed stamped envelope will be provided by the local site for the mailing of the signed consent form and all study assessment forms to the local clinical site. Participants can also opt to scan and email or text the signed consent form; however, participants cannot opt to scan and email or text study assessment forms. It is anticipated that there will be <10 participants per state which will keep site costs reasonable. Study assessment and data collection information are provided in subsequent sections.

All participants will complete pre- and post-intervention assessments with primary outcomes additionally assessed at mid-intervention (Week 7). The PHQ-9 and GAD-7 may be administered by telephone.

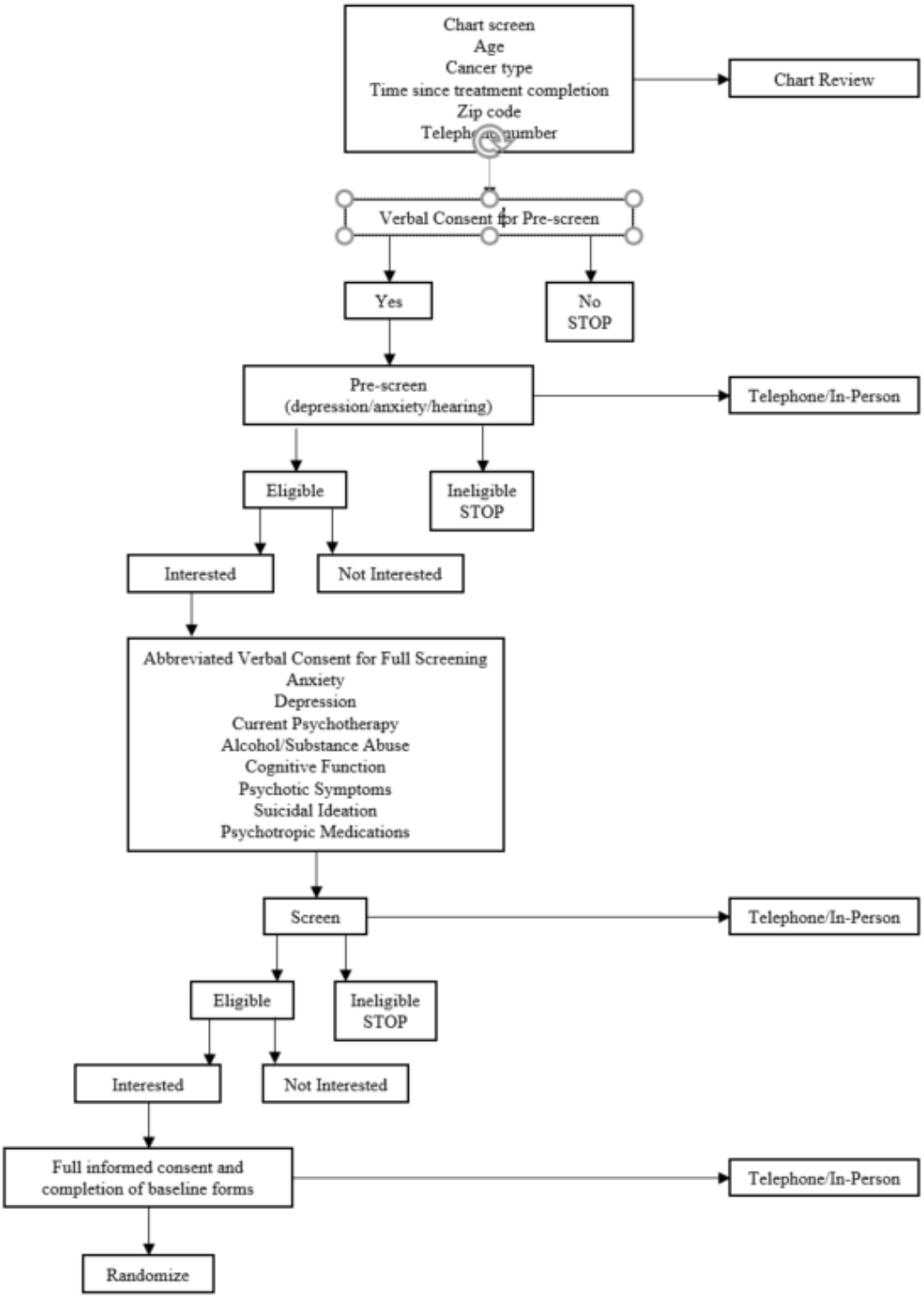
Participants receiving the high-intensity stepped-care telehealth intervention will be reminded during their last session that they will receive a post-intervention questionnaire packet via mail. Participants in the EUC group will receive an e-mail or telephone reminder (per their preference) that they will receive questionnaire packets via mail. If study questionnaires are not received within 2 weeks of the documented mail date, the NCORP site research staff will contact participants via telephone or email. If participants cannot be reached within 3 days by phone or email, the NCORP site research staff will mail another questionnaire packet. If there is still no response within two weeks of mailing the additional set of post-intervention questionnaires, participants will be contacted via phone and offered the opportunity to complete the post-intervention questionnaires by phone.

7.3 Baseline Testing/Pre-Study Evaluation

7.3.1. Rationale for Multi-Step Consent Process

We anticipate that a large proportion of the potential participants whom we screen may be ineligible for the study. To minimize burden and be most considerate of participants' time, we plan to implement a multi-step consent process as described below. Essentially, we will describe as much information as needed to obtain critical screening information and only fully explain the entire study to participants who meet eligibility criteria. In brief, we plan to proceed as follows (see schema below): (1) Prior to the pre-screening visit, the potential participant's name, contact information, demographics and chart information for eligibility criteria will be collected on a Pre-Visit Form (Appendix 2) that will be reviewed with potential participants during the pre-screening visit; (2) Brief pre-screening visit with a waiver of documentation of informed consent, a 3-item depression/anxiety screening, an item to determine adequate hearing ability, determine if they have access to a phone, understand English and review of the previously collected contact information, demographics and basic information about cancer diagnosis and treatment (enrollment criteria); (3) Full study screening with the Abbreviated Verbal Consent to include the full PHQ-9 and GAD-7. . The abbreviated consent will explain the screening process without details of the full study; and (4) Full informed consent will then take place for any potential participants who meet all eligibility criteria in the first two steps described here. If the participant is present in person, all of these steps may be completed in the same visit.

Schema of Three-Step Consent Process



7.3.2. **Pre-Visit Form**

For potential participants who are eligible to be contacted for the Pre-Screening visit, the Pre Visit Form will be completed on paper prior to the Pre-Screening visit to streamline the multistep screening process. This form includes their full name, contact information (phone number, address), 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, residency zip code). Sites should track Pre-Visit Form completion internally. This information will not be entered into the Telehealth website at the time this information is collected. It is important to retain contact information on the Pre-Visit Form so that sites can verify contact information during the Pre-Screening visit. This step is important when recruiting for a study of depression and anxiety as study staff may encounter someone who is suicidal and will need to take steps to ensure safety.

7.3.3. Pre-Screening

Referred participants will be invited to complete pre-screening for this study. If site staff are unable to make the initial pre-screening invite contact after 5 attempts, the referred participant will be considered a passive refusal and will no longer be contacted by site staff. If pre-screening is scheduled for a later date and the referred participant cannot be re-contacted after 5 attempts, the referred participant will be considered a passive refusal and will no longer be contacted by site staff. For referred participants who are considered a passive refusal, site staff will be asked to enter **only** race, ethnicity, cancer type, cancer stage, year of birth, and contact attempts into the Telehealth website.

Participants who accept the study invite will be asked to provide a verbal waiver of documentation of informed consent to complete pre-screening call or visit. If a participant provides verbal consent, the Pre-Visit 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, residency zip code). Participants will also be asked to complete the PHQ-2, 1 anxiety question, and additional questions to further pre-screen for 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 English language fluency. Pre-Screening information will be collected on paper forms. This information will not be entered into the Telehealth website at the time Pre-Screening information is collected.

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, staff will continue with screening. If the participant is unable to repeat after a second attempt or if staff thinks hearing is a problem, the participant is 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. It is suggested that participants who are screened at the site call the site staff from their cell phone or other site/clinic phone.

If someone declines pre-screening or is ineligible after pre-screening, no Protected Health Information (PHI) will be entered into the Telehealth website. For individuals who do not proceed to full screening, staff will be asked to enter **only** race, ethnicity, cancer type, cancer stage, and year of birth from the Pre-Visit Form into the Telehealth website. A PID will be assigned at this time. All information collected on the Pre-Screen Form will be entered in the Telehealth website.

If a participant meets the eligibility criteria based on responses to the questions and scores ≥ 2 on the PHQ-2 or ≥ 1 on the anxiety question, they will be invited to participate in the full screening assessment to determine eligibility for the study. In order to complete the full screening, sites will administer the abbreviated verbal consent. It is recommended that the screening immediately follow the pre-screening; however, there is no time limit between the Pre-Screening and Screening visits. For those who agree to the abbreviated verbal consent for full screening, all data from the Pre-Visit Form and Pre-Screening will be entered into the Telehealth website. A PID will be assigned at this time.

7.3.4. Full Screening

If a participant meets the eligibility criteria on the pre-screen, the participant will be asked to complete the Abbreviated Verbal Consent for full screening. Once a participant has agreed to the abbreviated verbal consent, emergency contact information will be collected and 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 PHQ-9 is a nine-item self-report measure used for screening, diagnosing, monitoring and measuring the severity of depression that incorporates DSM-IV depression diagnostic criteria. A score ≥ 8 indicates moderate depressive symptoms, and a score ≥15 suggests severe depressive symptoms

- The GAD-7 is a seven-item self-report measure that incorporates DSM-IV symptoms for generalized anxiety disorder. A score ≥ 10 indicates moderate anxiety symptoms, and a score ≥ 15 suggests severe symptoms.

All pre-screening and/or screening steps may be completed in one visit or phone call. If done in person, the anxiety question, PHQ-2, PHQ-9 and GAD-7 are to be interviewer administered, and there should not be any missing data on these forms.

Subjects who agree to the abbreviated verbal consent and do not complete the full screening at this time will be contacted up to 5 more times by the site staff. After 5 contact attempts the subject will be considered lost to follow-up and will be considered a screen fail, unless the subjects re-contacts the site. Site staff will enter any screening information collected in the Telehealth website.

Randomization must happen within 30 days of screening. If more than 30 days has passed, the full screening assessment should be re-administered.

7.3.5. Full Informed Consent

If the participant is eligible based on the screening visit responses and is willing to participate, the full informed consent for study participation should be administered.

If a participant is not eligible or declines study participation at screening, site staff will enter screening information in the Telehealth website up to the point the participant was no longer eligible or declined, and no further information will be collected.

7.4 Baseline Testing

If full informed consent was administered 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 site staff. Baseline Self-Administered Measures

may be completed by the participant at the site or site staff may choose to mail baseline self-administered measures to the participant with a request that they be returned as soon as possible and within two weeks (see Section 7.2). If the self-administered measures are mailed to a participant, site staff may call the participant to collect self-administered baseline responses by phone. Randomization must happen after baseline assessments but within 30 days of screening. Replacement packets can be mailed or emailed at participant request. The sites must receive the following self-administered completed forms from the participant prior to enrolling and randomizing the participant.

Self-Administered Measures (Appendix 5a/5b):

- Demographics and Health Behaviors
- Fear of Recurrence Inventory--Severity Subscale
- Insomnia Severity Index
- PROMIS – Fatigue Scale – Short Form 8a
- SF–36 Health Survey
- Impact of Events Scale–Revised
- Satisfaction with Medical/Mental Health services

Interviewer Administered Measures and Chart Review (Appendix 6):

NCORP component research staff will administer the following forms (see Appendices) by telephone (or in person if participant is in clinic) and enter the data on the study website **as the data are collected. 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)
- Charlson Comorbidity Index
- Cornell Services Index
- Current Medication Use

Chart Review:

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

7.5 Participant Enrollment and Randomization

The electronic participant enrollment form (Appendix 7) will be completed on the day of randomization in the Telehealth study website. The subject should not be randomized and enrollment form completed until the subject is ready to start the intervention. Review the Appendix 5a/5b (Baseline Self-Report Measures) for completeness before randomization. Once the participant is randomized, the study timeline begins. A participant will not be considered enrolled if they are not randomized to a study arm. Following randomization, the Randomization Form should be completed (Appendix 8).

7.6 Evaluation During Study Intervention

Weeks 1-12:

- **High Intensity Week 1/Low Intensity Week 2**: The Expectancy Rating Scale and instructions (Appendix 10a/b) will only be mailed to participants who are randomized to either the Low Intensity or the High Intensity intervention groups. Participants are to complete this Expectancy Rating Scale after they have completed Chapter 1 of the Cognitive Behavior Therapy Workbook.

- Enhanced Usual Care participants will not be mailed the Expectancy Rating Letter or Scale.
- Enhanced Usual Care participants will be mailed a "Thank You" letter at baseline (Support Document 6).
- Stepped-Care Telehealth (High Intensity) Progress Notes (Appendix 16)/Session Information Form (session completed Y/N) (Entered by therapist or NCORP component research staff on study website within 48 hours of therapy or check-in sessions)
- Telephone Script/Manual for Low Intensity Bi-Weekly (every two weeks) Check-In Call Form (Appendix 14).
- Implementation costs (tracking logs) (Appendix 24)

Week 7: (visit must be completed between Week 6 and Week 11)
NCORP component research staff will administer the following mid-intervention assessments by telephone and enter in the study website (Appendix 11).

- PHQ-9
- GAD-7
- Current Medication Use (Update)
- Adverse Event Ascertainment Form
- Mid-intervention letter mailed to Enhanced Usual Care participants only (Support Document 6).

7.7 Evaluation at Completion of Study Intervention – Week 13 (could occur weeks 13-15 only for High Intensity Participants): (visit must be completed between Week 12 and Week 15)

Self-Administered Measures (Appendix 12a/b):

Participants will be mailed the following self-report post-intervention measures with a request that they be returned within two weeks.

- Fear of Recurrence Inventory--Severity Subscale
- Insomnia Severity Index
- PROMIS Fatigue Scale- Short Form 8a
- SF-36 Health Survey
- Impact of Events Scale – Revised
- Client Satisfaction Questionnaire
- Working Alliance Inventory-Participant (high-intensity participants only)
- Expectancy Rating Scale (low intensity and high intensity participants only)

Interviewer Administered Measures and Chart Review (Appendix 13):

NCORP component research staff will administer the following post-intervention measures by telephone and enter on the study website:

- PHQ-9
- GAD-7
- Cornell Services Index
- Current Medication Use (Update)
- Adverse Event Ascertainment Form

Chart Review:

- Cancer Relapse/Recurrence Form

After all therapy sessions with each participant have been completed, the therapist will complete the Working Alliance Inventory-Therapist form (Appendix 17). The Working Alliance Inventory is a process measure to evaluate the potential impact of the telehealth intervention on the therapist-participant relationship.

7.8 End of Study

Upon completion of study visits, the Participant Completion Letter (Support Document 3) and the Resource Sheet (Support Document 9) will be mailed to participants in the Low Intensity and High Intensity groups.

7.9 Methods for Clinical Procedures

The Study Parameter Table (below) indicates the timing, mode of administration, and person who administers every aspect of the study.

Study Parameter Table

	Recruitment/ Chart Review	Pre-Screen	Verbal Consent	Full Screen	Full Informed Consent	Baseline	Enrollment/ Randomization (wk0)	Weeks 1-13			Post Week 13	Arm
								Wk1 or 2	W7	W13		
NCORP Component Site Staff Responsibility												
Mail Recruitment Documentation*	As needed											---
Pre-Visit Form (Appx 2)	X											---
Pre-Screening Form (Appx 3)*		X[a]										---
Abbreviated Verbal Consent			X[a]									---
Screening Form (Appx 4)*				X[a]								---
Full Informed Consent					X[a]							---
Baseline Self-Report Letter and Measures (Appxs 5a+b)*						X[a]						---
Baseline Interviewer-Administered Measures and Chart Review (Appx 6)*						X[a]						---
Letter to Ineligible Participants (SD 2)		As Needed										---
Enrollment Form (Appx 7)							X					---
Randomization Form (Appx 8)							X[b]					---
EUC Randomization*							X		X			EUC
Expectancy Rating Scale and Letter[44,45,64] (Appxs 10a+b)								X				LISC/ HISC
Low Intensity Check-In Call Form (Appx 14)								Biweekly (wks 2/4/6/8/10/12)				LISC
Upload audio recordings								Biweekly (wks 2/4/6/8/10/12)				LISC
Week 7 Mid-Assessment Interviewer-Administered Measures (Appx 11)*									X			All
Week 13 Self-Report Letter and Measures (Appxs 12a+b)*										X		All
Week 13 Interviewer-Administered Measures (Appx 13)*										X[c]		All
Participant Completion Letter (SD 3)/Resource Sheet (SD 9)											X	LISC/ HISC
Participant Change Status Form (Appx 23)								As Needed				All
Adverse Event Form (Appx 22)		As Needed										All
Crisis Protocol Event Form (Appx 21)		As Needed										All
Tracking Log (Appx 24)		To be completed for each attempted contact and actual contact										All
Wake Forest Research Base Responsibility												
EUC Randomization*							X					EUC
Investigator adherence rating forms (Appx 18 and 19)*								As needed				LISC/ HISC
Mail Recorder							As needed					LISC/ HISC
Mail CBT Booklet							X					LISC/ HISC
Mail CBT Booklet											X	EUC
Study Therapist Responsibility												
Weekly Therapist activities (Appxs 15-17) recordings*								Weekly (wks 1-13)				HISC
Tracking log		To be completed for each attempted contact and actual contact										HISC

Abbreviations: Appx=Appendix, EUC=Enhanced Usual Care, HISC=High-Intensity Stepped-Care Arm, LISC=Low-Intensity Stepped-Care Arm
** See appendix 26 for details*
[a] If participant is being seen in person, all of these steps can occur during one appointment
[b] Randomization should happen within 30 days of the full screen. If not, full screen (appx 4) will need to be re-administered
[c] For participants in the HISC arm, week 13 measures should be completed after the intervention is finished (could be weeks 13-15)
Note: Regarding potential participant burden, estimated times to complete study measures are as follows: pre-screen (5-10 minutes); screen (up to 20 minutes); participant measures at baseline and Week 13 (30-60 minutes); participant measures at Week 7 (5 minutes)
Note: See the Telehealth website for specific windows of when data should be collected post-randomization for each participant. The PHQ-9 and GAD-7 must be entered into the Telehealth website within 48 hours of administration. All other assessments should be entered within 14 days of the date assessments are completed unless otherwise specified.

8. CRITERIA FOR EVALUATION AND ENDPOINT DEFINITION

8.1 Primary Endpoint

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

Recruitment. To determine recruitment rate, we will track 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 (high-intensity intervention) or check-in (low-intensity intervention) sessions each participant completes.

The Working Alliance Inventory will be summarized with descriptive statistics to describe the therapist-participant relationship as a process measure

8.2 Secondary Endpoints

8.2.1. Depression and Anxiety Measures

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]

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]

8.2.2. Quality of Life and Symptom Measures:

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).

The **Insomnia Severity Index** (ISI)[56] is 7-item self-report measure of type and severity of insomnia symptoms, including problems with sleep onset, sleep maintenance, or early morning

awakening; satisfaction with current sleep pattern; interference with daily functioning; noticing impairment attributed to sleep problems; and level of concern or distress caused by the sleep problem. Responses are summed, with higher scores indicating greater sleep impairment. It has demonstrated reliability and validity in screening primary care patients for insomnia.[71]

The **PROMIS Fatigue Short Form**[72] is a measure of the experience of fatigue and the impact of fatigue on activities across multiple domains. Seven items are rated on a scale of 1(never) to 5 (always) based on how often it was experienced over the last 7 days.

The **SF-36**[59] is a self-report measure of quality of life consisting of 36 items that form 8 subscales: physical functioning, role limitations due to physical health problems, role limitations due to emotional health problems, social functioning, freedom from pain, energy or fatigue, emotional well-being, and general health perceptions. These 8 subscales are also combined into two domains: the Physical Component Summary (PCS) and the Mental Component Summary (MCS). All of these scales range from 0 (maximum impairment) to 100 (no impairment). All scales range from 0 (maximum impairment) to 100 (no impairment). It has demonstrated good internal validity and construct validity.[60,61]

The Impact of Events Scale – Revised (IES-R)[62,63] is a 22-item self-report measure of cancer-related distress. It is one of the most widely used measures of event-specific distress. The IES-R assesses the frequency with which respondents experience intrusive thoughts, avoidant behaviors, and autonomic arousal specific to one's thoughts and feelings about cancer over the past week.

8.2.3. Health Care Utilization

The **Cornell Services Index**[66] is a structured interview that assesses the frequency of use of medical outpatient visits, psychiatric and psychotherapeutic visits, and intensive services such as hospitalizations, emergency room visits, and home health visits. The services assessed in the Cornell Services Index are aggregated into outpatient psychiatric or psychological services, outpatient medical services, professional support services, and intensive services.

8.2.4. Implementation Costs

Tracking logs will measure the time spent in intervention-related activities such as bi-weekly check-in phone calls and therapy sessions with participants in stepped care, related to implementation. Tracking logs should be entered within 1-2 days of intervention-related activities; however, sites have up to 30 days to enter this information. NCORP Research Base Staff will keep an internal record of staff meetings, phone charges, mailing and printing costs and therapist training.

8.3 Off-Study Criteria

Participants may go 'off-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.

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 (Appendix 23) in the Telehealth website.

8.4 Study Termination

NCI/DCCPS as the study sponsor or the Wake Forest NCORP Research Base has the right to discontinue the study at any time.

9. CORRELATIVE/SPECIAL STUDIES- N/A

10. SPECIMEN MANAGEMENT- N/A

11. REPORTING ADVERSE AND SERIOUS ADVERSE EVENTS

11.1 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, in Telehealth, sites will report all serious adverse events (SAEs) described in Section 11.2 and selected AEs listed in Section 11.3.

SAEs and AEs will be ascertained by site staff for all participants at Weeks 7 and 13. Telehealth staff will administer the Adverse Event Ascertainment Form (Appendix 22) 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. SAEs occurring during the study should also be reported for all participants to CTEP-AERS (see section below).

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

11.2 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

Serious adverse events as described above must be reported on the Telehealth Adverse Event Form and also be reported to CTEP-AERS:

CTEP-AERS (Research Base Data Management) reporting timelines are defined as:

- Deaths or life threatening events (Grades 4-5): 24-Hour; 5 Calendar Days - The SAE must initially be reported via CTEP-AERS within 24 hours of learning of the SAE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- Hospitalizations, disabling, important medical events (IME) that may not result in death, be life threatening, or require hospitalization (Grade3) and study specific adverse events: 10 Calendar Days - A complete expedited report on the SAE must be submitted within 10 calendar days of learning of the SAE.

11.3 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.

11.3.1. 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). The computer software system will automatically generate an e-mail to the co-PIs and the project manager. 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.

12. STUDY MONITORING

12.1 Data Management

The Enrollment Form should be completed on-line at randomization. Data will be entered directly into the study website. The PHQ-9 and GAD-7 must be entered into the Telehealth website within 48 hours of being administered. The Crisis Protocol form (Appendix 21) must be entered into the Telehealth website at the time the form is completed with the participant. Refer to Section 11 for submitting the Adverse Event form. All other assessments must be completed within the designated study visit windows then data entered into the Telehealth website by designated site staff or designated study therapist within 14 days from the date assessments are completed.

12.2 Case Report Forms

Participant data will be collected using protocol-specific case report forms (CRF).

12.3 Source Documents

The sources of research material will include information provided through participant interviews, intervention sessions, and self-report questionnaires specifically for this research study. A number of steps will be taken to ensure the confidentiality of research data collected during the study. The study will obtain a Certificate of Confidentiality which prevents researchers from being forced to disclose identifying information by certain legal proceedings. All forms will be stored in locked file cabinets.

Names will be removed from all forms and records and replaced with participant numbers. Recorded sessions will be erased upon completion of data collection. Information stored in the computer will be password protected. Only members of the investigative team will have access to any participant information and data. The identities of participants will not be revealed in publications and presentations of any results from this project. Procedures specified in the consent form are consistent with HIPAA regulations. All investigators have completed NIH-required training in human subjects protection.

An investigator and other designated staff are required to prepare and maintain adequate and accurate documentation that records all observations and other data pertinent to the investigation for each individual participating in the study. All data recorded in the research record (including data recorded on CRFs) must originate in the participant's medical record, study record, or other official document sources.

Source documents substantiate CRF information. All participant case records (e.g., flow sheets, clinical records, physician notes, correspondence) must adhere to the following standards:

- Clearly labeled in accordance with HIPAA practices so that they can be associated with a particular participant identification number (PID);
- Legibly written in ink;
- Signed and dated in a real time basis by health care practitioner evaluating or treating the participant; and
- Correction liquid or tape must not be used in source documents or on CRFs.
- Corrections are made by drawing a single line through the error. Do not obliterate the original entry. Insert the correct information, initial, and date the entry.

12.4 Data and Safety Monitoring Plan

The Comprehensive Cancer Center Data Safety Monitoring Board meets every six months to review all phase II and phase III protocols. The Board includes members demonstrating experience and expertise in oncology, biological sciences, biostatistics, pastoral care/counseling, and ethics. The members of this committee as well as the organization statistician will oversee the safety monitoring of the study, ensure that the privacy of all participants in the study is protected and ensure that participants' interests are primary, that is, above the interests of the scientific investigation. Adverse events will be elicited by study staff during assessments and check-in calls for the EUC group and by the study therapists during each session. Information about any adverse events 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 NCI and WFUSM IRB.

12.5 Sponsor or FDA Monitoring

The NCI, DCCPS (or their designee) may audit various aspects of the study. This auditor will be given access to facilities, databases, supplies and records to review and verify data pertinent to the study. This protocol does not include pharmaceuticals or require FDA monitoring.

12.6 Record Retention

Clinical records for all participants, including CRFs, all source documentation (containing evidence to study eligibility, history and physical findings, laboratory data, results of consultations, *etc*.), as well as IRB records and other regulatory documentation will be retained by the Investigator in a secure storage facility in compliance with Health Insurance Portability and Accountability Act (HIPAA), Office of Human Research Protections (OHRP), Food and Drug Administration (FDA) regulations and guidances, and NCI/DCCPS requirements, unless the standard at the site is more stringent. The records for all studies performed under an IND will be maintained, at a minimum, for two years after the approval of a New Drug Application (NDA). For NCI/DCCPS, records will be retained for at least three years after the

completion of the research. NCI will be notified prior to the planned destruction of any materials. The records should be accessible for inspection and copying by authorized persons of the Food and Drug Administration. If the study is done outside of the United States, applicable regulatory requirements for the specific country participating in the study also apply.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Description

13.1.1. Primary Objectives

To determine feasibility (recruitment, accrual, retention, adherence) of a RCT of a stepped-care telehealth mental health intervention (tailored to symptom level) versus enhanced usual care in 90 post-treatment cancer survivors with moderate or severe levels of emotional distress (anxiety and/or depressive symptoms).

13.1.2. Secondary Objectives

To obtain preliminary data on the efficacy and variability of a stepped-care telehealth mental health intervention (tailored to symptom level) versus enhanced usual care for reducing emotional distress (anxiety and/or depressive symptoms) in 90 post-treatment cancer survivors.

To obtain preliminary data on the efficacy and variability of a stepped-care telehealth mental health intervention (tailored to symptom level) versus enhanced usual care for secondary outcomes (sleep disturbance, fatigue, fear of recurrence, cancer-related distress, and QOL) in 90 post-treatment cancer survivors.

To determine costs associated with both stepped-care telehealth and enhanced usual care interventions from the perspective of a healthcare provider. We will determine costs of intervention implementation and health care utilization in all arms over the course of the interventions.

13.1.3. Exploratory Objectives

To examine potential differential effects of the intervention on anxiety, depression, sleep disturbance, fatigue, fear of recurrence, and QOL, by gender, age, race/ethnicity, stratification arm (moderate, severe), and psychotropic medication use at baseline.

To examine mediating effects of expectancy ratings of the intervention on anxiety and depression.

13.2 Randomization/Stratification

Participants will be stratified by baseline score ≥15 on the GAD-7 and/or on the PHQ-9, indicating severe anxiety or depressive symptoms, and by whether they qualified for the study by the GAD-7, PHQ-9, or both. Participants with moderate symptoms only (8-14 on the PHQ-9 and <15 on the GAD-7 or 10-14 on the GAD-7 and <15 on the PHQ-9) will be randomized to either the low-intensity stepped-care telehealth or to the enhanced usual care (EUC control) with equal probability. Participants with severe symptoms will be randomized to either the high-intensity stepped-care telehealth intervention or the EUC control with equal probability. Participants randomized to the low-intensity stepped care telehealth arm who experience increased symptoms at week seven and now experience severe level of symptomatology will receive the high-intensity intervention (see Section 7.1). Analysis will proceed as intent-to-treat using

their initial stepped-care telehealth assignment; we do not anticipate that many people will change from moderate to severe during the study. We anticipate enrolling 45 patients in the stepped-care telehealth intervention and 45 in the enhanced usual care group. We will enroll 50 participants in the moderate symptom strata, and 40 participants in the severe symptom strata. Block sizes will be chosen randomly to ensure that future assignments cannot be inferred from previous ones.

13.3 Sample Size

The sample size (N=90) is based on goals of estimating retention, recruitment, adherence and accrual rates and effect sizes to inform design of a larger efficacy trial. If the drop-out rate is >30%, a larger study may not be feasible. With N=90, we are confident that this rate will be ≤30% when the observed drop-out rate is as large as 22% (upper limit of the one-sided 95% CI is 29.2%). Similarly, the lower limit of a one-sided 95% confidence interval for the recruitment rate can be estimated within 8.2% of the observed rate if we approach at least 100 participants to recruit 90, and the lower limit of a one-sided 95% confidence interval for the adherence can be estimated within 8.7% of the observed rate with N=90. Using the normal approximation to the Poisson, we can estimate the lower limit of the one-sided 95% confidence interval of the accrual rate within approximately 2 people per month if the observed rate is 11 people per month. To compare differences between the groups on changes in the PHQ-9 and GAD-7 scores, we can estimate the intervention effect within ±0.46 SD with a sample size of 36/group (stepped-care telehealth, enhanced usual care), allowing 20% dropout of the 45/group randomized. This corresponds to 2.7 points on PHQ-9 and 1.9 points on GAD-7 using SDs from studies of change in the measures of 5.8 and 4.2 points, respectively.[51,73–75]

13.4 Primary Objective, Endpoint(s), Analysis Plan

For Objective 1.1.1, recruitment, accrual, retention, and adherence rates will be calculated. To determine the recruitment rate, we will track number of eligible participants and percent who agree to participate. Accrual rates will be calculated by calculating the mean number of participants recruited per month. Study retention will be estimated by the proportion of participants who complete the Week 7 and 13 visits. Intervention adherence will be estimated as the mean percentage of therapy or check-in sessions each participant completes. Drop-out is defined as 100% minus the dropout %. 95% confidence intervals will be calculated for each measure to quantify uncertainty in the estimates and to determine if the lower (recruitment, accrual) or upper (retention, adherence) limit would indicate lack of feasibility for future work.

13.5 Secondary Objectives, Endpoints, Analysis Plans

For Objective 1.2.1, baseline descriptive statistics will be compared by intervention arm using chi-square tests for categorical variables and ANOVA for continuous variables. Due to randomization, we do not anticipate differences by intervention arm; if they are found, we will adjust for them in the analyses for Objectives 1.2.1, 1.2.2, 1.2.3, and 1.2.4. The Working Alliance Inventory will be summarized using descriptive statistics.

Depression and anxiety outcomes (PHQ-9 and GAD-7) will be analyzed using mixed-model analysis of covariance (ANCOVA) to account for intra-individual correlations among longitudinal measures. The model will contain terms for the intervention group, baseline value of the outcome, therapist or site staff person completing check-in calls, psychotropic medications use, a time effect (mid-, post-intervention), and the time by intervention interaction term (to test whether the intervention effects vary by time). Because participants may exhibit moderate or severe levels of either depression or anxiety, we will create a combined variable that indicates if a participant had moderate/severe depression or anxiety at mid- or post-intervention. Each stepped-care telehealth group will be compared with EUC using a GEE approach with a logit link to determine if rates of the combined outcome differ at mid- or post-intervention. Other outcome measures (sleep disturbance, fatigue, fear of recurrence, cancer-related distress, and quality of life) will be analyzed using ANCOVA at week 13 to meet objective 1.2.2.

For Objective 1.2.3, we will calculate total cost of the stepped-care telehealth (low intensity, high intensity) and the EUC interventions and average cost/survivor screened and randomized to each trial arm. Total cost includes costs of intervention implementation and health care costs for each participant.

Implementation costs will be determined using data on time spent on intervention activities reported in the tracking logs. Time spent on the intervention includes i) training personnel to screen and deliver the intervention including time of trainer and trainees; ii) time spent by interventionists on intervention activities, including screening, scheduling and delivering the phone sessions, and documenting contacts/progress; iii) phone charges; and iv) other supply costs (e.g., CBT workbooks). Cost of time will be valued using wage rates based on national averages for research staff and psychotherapists. Other costs (e.g., telephone charges and printed materials) will be valued using project records on expenses incurred. We will sum all costs related to each intervention to obtain the total cost of implementing each. Total costs in each study arm will be dividing by the number of patients served to obtain the average cost per patient. Sensitivity analyses will be conducted to assess how implementation costs vary depending on the inputs used, such as the salaries of interventionists or supervisors.

Health care cost will be determined using data from self-reported utilization of heath care services (Cornell Services Index).[66] To calculate the costs related to these health care events, we will use published data on average costs of these events or data from sources such as the Medicare Fee Schedule and/or the Medical Expenditure Panel Survey. We will conduct analyses to examine the impact of the stepped-care interventions on health care utilization and costs: similar to analyses specified above for Objective 1.2.1, we will use linear models with utilization or costs as the dependent variable, and the arm assignment as the independent variable. Because the distribution of costs is usually skewed, we will consider using a generalized linear model with a gamma link.

13.6 Exploratory Objectives, Endpoints, Analysis Plans

We will perform stratified subgroup analysis of the outcomes in Objectives 1.2.1 and 1.2.2. by gender, age, race/ethnicity, stratification arm (moderate, severe), and psychotropic medication use at baseline to meet Objective 1.3.1 using ANCOVA at week 13. To analyze Objective 1.3.2, we will use a mediation approach to examine whether expectancy ratings mediate the relationship between the intervention and the outcomes of interest (PHQ-9, GAD-7, or the combined outcome) at the intervention mid-point or end. First, we will examine whether the expectancy rating score is a significant predictor of the outcome in the mixed-model analysis of covariance (ANCOVA) model with terms for the expectancy rating score, baseline value of the outcome, therapist or site staff person conducting check-in calls, psychotropic medications use, a time effect (mid-, post-intervention), and the time by intervention expectancy score term (to test whether the expectancy score effects vary by time). Then we will fit the same model with the intervention effect, expectancy rating score, and their interactions with each other and time. If the effect for the mediator is significant in this model and the parameter estimate of the intervention effect is smaller than in the analysis of Objective 1.2.1 it will indicate evidence of mediation.

13.7 Reporting and Exclusions

Unless we receive written or verbal withdrawal of consent, we will try to reach every participant for telephone calls, telephone sessions, and assessments as outlined in the protocol.

The dataset used in the analysis of Objective 1.1.1 will include all eligible participants to calculate recruitment rates. Accrual, retention, and adherence will be calculated on the participants who consent to participate in the study. The analysis of the secondary objectives and exploratory objective will include all participants who consent to participate in the study. The ANOVA models used for the secondary objectives use data from all available time points and allows for data to be missing at random. For the analyses of the secondary objectives and the exploratory objective, we will use an intent-to-treat approach. If participants are moved from low intensity to high intensity they will be analyzed using the

low intensity assignment (intent to treat). In exploratory models, we will analyze the impact of adherence by including it as a predictor.

13.8 Evaluation of Response

All participants in the study who complete the PHQ-9 and GAD-7 at Week 13 will be evaluable for response to the intervention. In sensitivity analyses, we will evaluate how imputation of these values utilizing either baseline or Week 7 data impact study conclusions. Note that this is a feasibility study and analyses of the intervention effects will be used to plan future studies, not to demonstrate efficacy.

REFERENCES

1. Armes J, Crowe M, Colbourne L, Morgan H, Murrells T, Oakley C, Palmer N, Ream E, Young A, Richardson A. Patients' supportive care needs beyond the end of cancer treatment: a prospective, longitudinal survey. *JClinOncol*. 2009;27(1527-7755 (Electronic)):6172-6179.

2. Alfano CM, Rowland JH. Recovery issues in cancer survivorship: a new challenge for supportive care. *Cancer J*. 2006;12(1528-9117 (Print)):432-443.

3. Hodgkinson K, Butow P, Fuchs A, Hunt GE, Stenlake A, Hobbs KM, Brand A, Wain G. Long-term survival from gynecologic cancer: psychosocial outcomes, supportive care needs and positive outcomes. *GynecolOncol*. 2007;104(0090-8258 (Print)):381-389.

4. Jacobsen PB, Donovan KA, Swaine ZN. Management of anxiety and depression in adult cancer patients: Toward an evidence-based approach. In: Chang AE, Ganz PA, Hayes DF, eds. *Oncology: An Evidence-Based Approach*. Philadelphia, PA: Springer; 2006:1552-1579.

5. Jefford M, Karahalios E, Pollard A, Baravelli C, Carey M, Franklin J, Aranda S, Schofield P. Survivorship issues following treatment completion--results from focus groups with Australian cancer survivors and health professionals. *JCancer Surviv*. 2008;2(1932-2267 (Electronic)):20-32. doi:10.1007/s11764-008-0043-4.

6. Stanton AL, Bower JE, Low CA. Posttraumatic Growth After Cancer; Handbook of Posttraumatic Growth: Research and Practice. In: G.Calhoun, R.G.Tedeschi, eds. *Handbook of Posttraumatic Growth: Research and Practice*. Mahway, NJ: Lawrence Erlbaum Associates; 2006:138-175.

7. Andersen BL, Yang HC, Farrar WB, Golden-Kreutz DM, Emery CF, Thornton LM, Young DC, Carson WE III. Psychologic intervention improves survival for breast cancer patients: a randomized clinical trial. *Cancer*. 2008;113(0008-543X (Print)):3450-3458. doi:10.1002/cncr.23969.

8. Den Oudsten BL, Van Heck GL, Van der Steeg AF, Roukema JA, De VJ. Predictors of depressive symptoms 12 months after surgical treatment of early-stage breast cancer. *Psychooncology*. 2009;18(1099-1611 (Electronic)):1230-1237. doi:10.1002/pon.1518.

9. Ganz PA, Kwan L, Stanton AL, Krupnick JL, Rowland JH, Meyerowitz BE, Bower JE, Belin TR. Quality of life at the end of primary treatment of breast cancer: first results from the moving beyond cancer randomized trial. *J NatlCancer Inst*. 2004;96(1460-2105 (Electronic)):376-387.

10. Kim SH, Son BH, Hwang SY, Han W, Yang JH, Lee S, Yun YH. Fatigue and depression in disease-free breast cancer survivors: prevalence, correlates, and association with quality of life. *J PainSymptomManage*. 2008;35(0885-3924 (Print)):644-655. doi:10.1016/j.jpainsymman.2007.08.012.

11. Philip EJ, Merluzzi TV, Zhang Z, Heitzmann CA. Depression and cancer survivorship: importance of coping self-efficacy in post-treatment survivors. *Psychooncology*. 2013;22(1099-1611 (Electronic)):987-994. doi:10.1002/pon.3088.

12. Punnen S, Cowan JE, Dunn LB, Shumay DM, Carroll PR, Cooperberg MR. A longitudinal study of anxiety, depression and distress as predictors of sexual and urinary quality of life in men with prostate cancer. *BJUInt*. 2013;112(1464-410X (Electronic)):E67-E75. doi:10.1111/bju.12209.

13. Scheffold K, Mehnert A, Muller V, Koch U, Harter M, Vehling S. Sources of meaning in cancer patients - influences on global meaning, anxiety and depression in a longitudinal study. *EurJ Cancer Care Engl*. 2014;23(1365-2354 (Electronic)):472-480. doi:10.1111/ecc.12152.

14. Vahdaninia M, Omidvari S, Montazeri A. What do predict anxiety and depression in breast cancer patients? A follow-up study. *Soc Psychiatry PsychiatrEpidemiol*. 2010;45(1433-9285 (Electronic)):355-361.

15. Jacobsen PB, Jim HS. Psychosocial interventions for anxiety and depression in adult cancer patients: achievements and challenges. *CA Cancer JClin*. 2008;58(0007-9235 (Print)):214-230.

16. Ristvedt SL, Trinkaus KM. Trait anxiety as an independent predictor of poor health-related quality of life and post-traumatic stress symptoms in rectal cancer. *BrJHealth Psychol*. 2009;14(1359-107X (Print)):701-715.

17. Brown LF, Kroenke K, Theobald DE, Wu J, Tu W. The association of depression and anxiety with health-related quality of life in cancer patients with depression and/or pain. *Psychooncology*. 2010;19(1099-1611 (Electronic)):734-741. doi:10.1002/pon.1627.

18. Deimling GT, Bowman KF, Sterns S, Wagner LJ, Kahana B. Cancer-related health worries and psychological distress among older adult, long-term cancer survivors. *Psychooncology*. 2006.

19. Diefenbach M, Mohamed NE, Horwitz E, Pollack A. Longitudinal associations among quality of life and its predictors in patients treated for prostate cancer: the moderating role of age. *PsycholHealth Med*. 2008;13(1354-8506 (Print)):146-161. doi:10.1080/13548500701352008.

20. Sharma N, Hansen CH, O'Connor M, Thekkumpurath P, Walker J, Kleiboer A, Murray G, Espie C, Storey D, Sharpe M, Fleming L. Sleep problems in cancer patients: prevalence and association with distress and pain. *Psychooncology*. 2012;21(1099-1611 (Electronic)):1003-1009. doi:10.1002/pon.2004.

21. Trudel-Fitzgerald C, Savard J, Ivers H. Which symptoms come first? Exploration of temporal relationships between cancer-related symptoms over an 18-month period. *Ann Behav Med*. 2013;45(1532-4796 (Electronic)):329-337. doi:10.1007/s12160-012-9459-1.

22. Satin JR, Linden W, Phillips MJ. Depression as a predictor of disease progression and mortality in cancer patients: a meta-analysis. *Cancer*. 2009;115(0008-543X (Print)):5349-5361. doi:10.1002/cncr.24561.

23. Pinquart M, Duberstein PR. Depression and cancer mortality: a meta-analysis. *PsycholMed*. 2010;40(1469-8978 (Electronic)):1797-1810. doi:10.1017/S0033291709992285.

24. Hewitt ME. National Cancer Policy Board (U.S.), & Committee on cancer survivorship: Improving care and quality of life. *Inst Med*. 2007.

25. Rowland JH, Hewitt M, Ganz PA. Cancer survivorship: a new challenge in delivering quality cancer care. *JClinOncol*. 2006;24(1527-7755 (Electronic)):5101-5104.

26. Carlson LE, Bultz BD. Benefits of psychosocial oncology care: improved quality of life and medical cost offset. *Health QualLifeOutcomes*. 2003;1(1477-7525 (Electronic)):8.

27. Weaver KE, Geiger AM, Lu L, Case LD. Rural-urban disparities in health status among US cancer survivors 3055. *Cancer*. 2013;119(1097-0142 (Electronic)):1050-1057. doi:10.1002/cncr.27840.

28. Burris JL, Andrykowski M. Disparities in mental health between rural and nonrural cancer survivors: a preliminary study. *Psychooncology*. 2010;19(1099-1611 (Electronic)):637-645. doi:10.1002/pon.1600.

29. Andrykowski MA, Burris JL. Use of formal and informal mental health resources by cancer survivors: differences between rural and nonrural survivors and a preliminary test of the theory of planned behavior. *Psychooncology*. 2009.

30. Stamm BH, Piland NF, Lambert D, Speck NC. A Rural Perspective on Health Care for the Whole Person. *Prof Psychol Res Pract*. 2007;38(3):298-304.

31. *American Psychological Association (2001). Caring for the Rural Community: 2000-2001 Report*.; 2001.

32. Brenes GA, Danhauer SC, Lyles MF, Hogan PE, Miller ME. Telephone-Delivered Cognitive Behavioral Therapy and Telephone-Delivered Nondirective Supportive Therapy for Rural Older Adults With Generalized Anxiety Disorder: A Randomized Clinical Trial. *JAMA Psychiatry*. 2015;72(10):1012-1020. doi:10.1001/jamapsychiatry.2015.1154.

33. United States Department of Agriculture. *USDA Economic Research Service - Rural Urban Continuum Codes Documentation*.; 2014. _http://www.ers.usda.gov/data-products/rural-urban-continuum-codes/documentation.aspx#.UurEFrQglhk_. Accessed January 30, 2014.

34. Welsh KA, Breitner JCS, Magruder-Habib KM. Detection of dementia in the elderly using telephone screening of cognitive status. *Neuropsychiatry Neuropsychol Behav Neurol*. 1993;(6):103-110.

35. Stanley MA, Beck JG, Glassco JD. Treatment of generalized anxiety in older adults: A preliminary comparison of cognititive-behavior and supportive approaches. *Behav Ther*. 1996;27:565-581.

36. Stanley MA, Hopko DR, Diefenbach GJ, Bourland SL, Rodriguez H, Wagener P. Cognitive-behavior therapy for late-life generalized anxiety disorder in primary care: preliminary findings. *Am J Geriatr Psychiatry*. 2003;11(1064-7481 (Print)):92-96.

37. Kroenke K, Theobald D, Norton K, Sanders R, Schlundt S, McCalley S, Harvey P, Iseminger K, Morrison G, Carpenter JS, Stubbs D, Jacks R, Carney-Doebbeling C, Wu J, Tu W. The Indiana Cancer Pain and Depression (INCPAD) trial Design of a telecare management intervention for cancer-related symptoms and baseline characteristics of study participants. *Gen Hosp Psychiatry*. 2009;31(1873-7714 (Electronic)):240-253. doi:10.1016/j.genhosppsych.2009.01.007.

38. Badger T, Segrin C, Pasvogel A, Lopez AM. The effect of psychosocial interventions delivered by telephone and videophone on quality of life in early-stage breast cancer survivors and their supportive partners. *J TelemedTelecare*. 2013;19(1758-1109 (Electronic)):260-265. doi:10.1177/1357633X13492289.

39. Meneses K, McNees P, Azuero A, Loerzel VW, Su X, Hassey LA. Preliminary evaluation of psychoeducational support interventions on quality of life in rural breast cancer survivors after primary treatment. *Cancer Nurs*. 2009;32(1538-9804 (Electronic)):385-397.

doi:10.1097/NCC.0b013e3181a850e6.

40. Freeman LW, White R, Ratcliff CG, Sutton S, Stewart M, Palmer JL, Link J, Cohen L. A randomized trial comparing live and telemedicine deliveries of an imagery-based behavioral intervention for breast cancer survivors: reducing symptoms and barriers to care. *Psychooncology*. 2014;(1099-1611 (Electronic)). doi:10.1002/pon.3656.

41. Head BA, Studts JL, Bumpous JM, Gregg JL, Wilson L, Keeney C, Scharfenberger JA, Pfeifer MP. Development of a telehealth intervention for head and neck cancer patients. *TelemedJ EHealth*. 2009;15(1556-3669 (Electronic)):44-52. doi:10.1089/tmj.2008.0061.

42. Zernicke KA, Campbell TS, Speca M, McCabe-Ruff K, Flowers S, Carlson LE. A randomized wait-list controlled trial of feasibility and efficacy of an online mindfulness-based cancer recovery program: the eTherapy for cancer applying mindfulness trial. *Psychosom Med*. 2014;76(1534-7796 (Electronic)):257-267. doi:10.1097/PSY.0000000000000053.

43. *U.S. Census Bureau, 2000. US Population Living in Urban vs. Rural Areas*.; 2000.

44. Barlow DH, Rapee RM, Brown TA. Behavioral treatment of generalized anxiety disorder. *Behav Ther*. 1992;23(4):551-571.

45. Clark DM, Salkovskis PM, Hackmann A, Wells A, Ludgate J, Gelder M. Brief cognitive therapy for panic disorder: a randomized controlled trial. *JConsult ClinPsychol*. 1999;67(0022-006X (Print)):583-589.

46. Larsen DL, Attkisson CC, Hargreaves WA, Nguyen TD. Assessment of client/patient satisfaction: development of a general scale. *Eval ProgramPlann*. 1979;2(0149-7189 (Print)):197-207.

47. Akkerman R, Stanley M, Averill P, Novy D, Snyder A, Diefenbach G. Recruiting Older Adults With Generalized Anxiety Disorder. *J Ment Health Aging*. 2001;7:385-394.

48. Tracey TJ, Kokotovic AM. Factor structure of the Working Alliance Inventory. *Psychol Assess*. 1989;(1):207-210.

49. Hewitt ME, National Cancer Policy Board (U.S.), Committee on Cancer Survivorship: Improving Care and Quality of Life. *From Cancer Patient to Cancer Survivor : Lost in Transition*. Washington, D.C.: National Academies Press,; 2006.

50. Busseri MA, Tyler JD. Interchangeability of the Working Alliance Inventory and Working Alliance Inventory, Short Form. *PsycholAssess*. 2003;15(1040-3590 (Print)):193-197.

51. Titov N, Dear BF, McMillan D, Anderson T, Zou J, Sunderland M. Psychometric comparison of the PHQ-9 and BDI-II for measuring response during treatment of depression. *Cogn Behav Ther*. 2011;40(1651-2316 (Electronic)):126-136. doi:10.1080/16506073.2010.550059.

52. Luckett T, Butow PN, King MT, Oguchi M, Heading G, Hackl NA, Rankin N, Price MA. A review and recommendations for optimal outcome measures of anxiety, depression and general distress in studies evaluating psychosocial interventions for English-speaking adults with heterogeneous cancer diagnoses. *Support Care Cancer*. 2010;18(1433-7339 (Electronic)):1241-1262.

53. Spitzer RL, Kroenke K, Williams JB, Lowe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. *ArchInternMed*. 2006;166(0003-9926 (Print)):1092-1097.

54. Seo EH, Lee DY, Kim SG, Kim KW, Kim do H, Kim BJ, Kim MD, Kim SY, Kim YH, Kim JL, Kim JW, Moon SW, Park JH, Ryu SH, Yoon JC, Lee NJ, Lee CU, Jhoo JH, Choo LH, Woo JI. Validity of the telephone interview for cognitive status (TICS) and modified TICS (TICSm) for mild cognitive imparment (MCI) and dementia screening. *Arch Gerontol Geriatr*. 2011;52(1872-6976 (Electronic)):e26-e30. doi:10.1016/j.archger.2010.04.008.

55. Simard S, Savard J. Fear of Cancer Recurrence Inventory: development and initial validation of a multidimensional measure of fear of cancer recurrence. *Support Care Cancer Off J Multinatl Assoc Support Care Cancer*. 2009;17(3):241-251. doi:10.1007/s00520-008-0444-y

56. Bastien CH, Vallieres A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. *Sleep Med*. 2001;2(1878-5506 (Electronic)):297-307.

57. Morin CM, Belleville G, Belanger L, Ivers H. The Insomnia Severity Index: psychometric indicators to detect insomnia cases and evaluate treatment response. *Sleep*. 2011;34(1550-9109 (Electronic)):601-608.

58. Cella D, Gershon R. *PROMIS Assessment Center User Manual Version 6.0*.; 2010. _www.nihpromis.org_.

59. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *MedCare*. 1992;30(0025-7079 (Print)):473-483.

60. McHorney CA, Ware JE Jr, Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. *MedCare*. 1993;31(0025-7079 (Print)):247-263.

61. McHorney CA, Ware JE Jr, Lu JF, Sherbourne CD. The MOS 36-item Short-Form Health Survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups. *MedCare*. 1994;32(0025-7079 (Print)):40-66.

62. Weiss D. The Impact of Events Scale-Revised. In: *Assessing Psychological Trauma and PTSD: A Practitioner's Handbook*. 2nd ed. New York: Guilford Press; 2007:168-189.

63. Salsman JM, Schalet BD, Andrykowski MA, Cella D. The impact of events scale: a comparison of frequency versus severity approaches to measuring cancer-specific distress. *Psychooncology*. 2015;24(12):1738-1745. doi:10.1002/pon.3784.

64. Borkovec TD, Nau SD. Credibility of analogue therapy rationales. *Behav Ther Exp Psychiatry*. 1972;3(257):260.

65. Horvath AO, Greenberg LS. Development and validation of the Working Alliance Inventory. *J Couns Psychol*. 1989;36:223-233.

66. Sirey JA, Meyers BS, Teresi JA, Bruce ML, Ramirez M, Raue PJ, Perlick DA, Holmes D. The Cornell Service Index as a measure of health service use. *Psychiatr Serv*. 2005;56(1075-2730 (Print)):1564-1569. doi:10.1176/appi.ps.56.12.1564.

67. Weaver KE, Aziz NM, Arora NK, Forsythe LP, Hamilton AS, Oakley-Girvan I, Keel G, Bellizzi KM, Rowland JH. Follow-up care experiences and perceived quality of care among

long-term survivors of breast, prostate, colorectal, and gynecologic cancers. *J OncolPract*. 2014;10(1935-469X (Electronic)):e231-e239. doi:10.1200/JOP.2013.001175.

68. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med*. 2001;16(0884-8734 (Print)):606-613.

69. Hinz A, Mehnert A, Kocalevent R-D, Brähler E, Forkmann T, Singer S, Schulte T. Assessment of depression severity with the PHQ-9 in cancer patients and in the general population. *BMC Psychiatry*. 2016;16:22. doi:10.1186/s12888-016-0728-6.

70. Lowe B, Decker O, Muller S, Brahler E, Schellberg D, Herzog W, Herzberg PY. Validation and standardization of the Generalized Anxiety Disorder Screener (GAD-7) in the general population. *MedCare*. 2008;46(0025-7079 (Print)):266-274.

71. Gagnon C, Bélanger L, Ivers H, Morin CM. Validation of the Insomnia Severity Index in primary care. *J Am Board Fam Med JABFM*. 2013;26(6):701-710. doi:10.3122/jabfm.2013.06.130064.

72. Garcia SF, Cella D, Clauser SB, Flynn KE, Lad T, Lai J-S, Reeve BB, Smith AW, Stone AA, Weinfurt K. Standardizing patient-reported outcomes assessment in cancer clinical trials: a patient-reported outcomes measurement information system initiative. *J Clin Oncol Off J Am Soc Clin Oncol*. 2007;25(32):5106-5112. doi:10.1200/JCO.2007.12.2341.

73. Lowe B, Unutzer J, Callahan CM, Perkins AJ, Kroenke K. Monitoring depression treatment outcomes with the patient health questionnaire-9. *Med Care*. 2004;42(0025-7079 (Print)):1194-1201.

74. Pilkonis PA, Yu L, Dodds NE, Johnston KL, Maihoefer CC, Lawrence SM. Validation of the depression item bank from the Patient-Reported Outcomes Measurement Information System (PROMIS) in a three-month observational study. *J PsychiatrRes*. 2014;56(1879-1379 (Electronic)):112-119. doi:10.1016/j.jpsychires.2014.05.010.

75. Dear BF, Titov N, Sunderland M, McMillan D, Anderson T, Lorian C, Robinson E. Psychometric comparison of the generalized anxiety disorder scale-7 and the Penn State Worry Questionnaire for measuring response during treatment of generalised anxiety disorder. *Cogn Behav Ther*. 2011;40(1651-2316 (Electronic)):216-227. doi:10.1080/16506073.2011.582138.

76. Thekkumpurath P, Walker J, Butcher I, et al: Screening for major depression in cancer outpatients: The diagnostic accuracy of the 9-item patient health questionnaire. Cancer 117:218-227, 2011

77. Manea L, Gilbody S, McMillan D: Optimal cut-off score for diagnosing depression with the Patient Health Questionnaire (PHQ-(): A meta-analysis. CMAJ 184:E191-E196, 2012