Protocol: Randomized Controlled Trial of Acceptance and Commitment Therapy for Fatigue Interference with Functioning in Metastatic Breast Cancer

Last approval date: 8/20/2024

1.0 Study Objectives

The primary objective of this NCI-funded Phase II RCT is to build on our pilot work by testing the impact of our telephone-based Acceptance and Commitment Therapy (ACT) program on fatigue interference (i.e., the degree to which fatigue negatively affects activities, mood, and cognition) in metastatic breast cancer (MBC) patients. A telephone-based approach can be readily disseminated to geographically dispersed patients and those with significant symptom burden and functional impairment that limit their ability to access in-person treatments. We will randomly assign MBC patients (N = 250) with significant fatigue interference to (1) six weekly 50-minute telephone sessions of ACT or (2) six weekly 50-minute telephone sessions of an education/support condition. Outcomes will be assessed at baseline, 2 weeks post-intervention, and 3 and 6 months post-intervention. Additionally, we will assess potential theory-driven mediators of the ACT intervention's effects. The study objectives are:

1.1 Primary Objective: To test the effect of telephone-based ACT on fatigue interference in MBC patients.

H1: ACT will lead to an improved primary outcome of fatigue interference as compared to education/support.

1.2 Secondary Objectives:

(a) To test the effects of telephone-based ACT on sleep interference, engagement in daily activities, and quality of life (QoL) in MBC patients.
H2: ACT will lead to improved secondary outcomes of sleep interference, engagement in daily activities, and QoL as compared to education/support.

(b) To examine change in psychological flexibility as a mediator of ACT's effect on fatigue interference.
H3: Increases in psychological flexibility will mediate the beneficial effect of ACT on fatigue interference.

1.3 Exploratory Objective:

To explore changes in the two core aspects of psychological flexibility (i.e., mindfulness/acceptance and commitment/behavior change processes) as mediators of ACT's effect on fatigue interference.

2.0 Outcome Measures/Endpoints

All outcomes will be assessed at baseline and 2 weeks, 3 months, and 6 months post-intervention.

2.1 Primary Outcome Measure:

The primary outcome measure is the 7-item Fatigue Interference subscale of the Fatigue Symptom Inventory.[1, 2]

2.2 Secondary Outcome Measures:

(1) Sleep interference will be assessed with the 8-item PROMIS sleep-related impairment measure.[3, 4] This measure assesses the perceived interference of sleep problems with activities, mood, and cognition.

(2) Engagement in daily activities will be assessed with the 6-item PROMIS short-form measure of ability to participate in social roles and activities.[5] The items,

which are reverse-coded, measure difficulty engaging in social and recreational activities as well as usual work (including housework).

(3) QoL will be measured with the 27-item FACT-G,[6] consisting of four subscales: Physical Well-Being, Social/Family Well-Being, Emotional Well-Being, and Functional Well-Being. An overall score is computed to represent general QoL.

3.0 Eligibility Criteria

3.1 Inclusion Criteria:

- Patient is at least 3 weeks post-diagnosis of stage IV breast cancer and is receiving care at the Indiana University Simon Cancer Center, Eskenazi Health, IU Health North, IU Health Bloomington, IU Health Ball Memorial, IU Health Portland, IU Health Morgan, IU Health New Castle, IU Health Central-Fishers, another IU Health hospital or clinic, Community Health Network, or the Robert H. Lurie Comprehensive Cancer Center of Northwestern University.
- Patient is at least 18 years of age.
- Patient has adequate English fluency for completion of data collection.
- Patient is willing to participate in this study.
- Patient has moderate to severe fatigue interference (i.e., mean score $\geq$2.5 on the Fatigue Interference subscale of the Fatigue Symptom Inventory)

3.2 Exclusion Criteria:

- Patient makes 3 or more errors on a validated 6-item cognitive screener[7] or exhibits significant psychiatric or cognitive impairment (dementia/delirium, intellectual disability, active psychosis) that in the judgment of the investigators would preclude providing informed consent and study participation.
- Patient Generated Subjective Global Assessment (PG-SGA; the patient-reported version of the Eastern Cooperative Oncology Group score) >2.
- Patient is receiving hospice care at screening.
- Patient does not have working phone service.
- Patient has hearing impairment that precludes participation.
- Male
- Patient was randomized to a study condition in protocol #1512252646 (a pilot version of the current trial)

Note: Patients who enroll in hospice during the trial will have the option of continuing trial participation.

4.0 Study Design

The study procedures are shown in **Table 1**. MBC patients (N = 250) who meet eligibility criteria and provide informed consent will be randomized to receive either six weekly sessions of the ACT intervention or the education/support condition. Outcomes will be assessed via telephone at baseline and approximately 2 weeks, 3 months, and 6 months post-intervention.

Table 1

Timing	Procedure and person(s) responsible
At least 3 weeks after the patient's Stage IV breast cancer diagnosis	(1) The potential participant will receive a letter by mail notifying them about the study. Anyone interested will be invited to call for more details. The letter will have an "opt out" component; thus, patients who are not interested in the study may call the study team to indicate that they do not wish to be contacted. The mailing will also include copies of the recruitment brochure, study consent form, and authorization form.
	(2) A research assistant will call all those who do not opt out to provide an overview of the study and screen interested MBC patients for eligibility. The research assistant will obtain verbal informed consent for study participation from interested and eligible patients (see "recruitment process" and "informed consent process" below).
Target date = within approximately 1 week after recruitment. The baseline assessment can be completed up to 1 month after recruitment.	(3) Patients who consent to participate will complete a baseline assessment over the phone (see "interview procedures" below). This interview will be administered by a trained research assistant or a trained doctoral student in clinical psychology.
Sessions will occur approximately 1 week from each other, with the first session occurring about 1 week following the baseline assessment. Participants will have up to 12 weeks to complete the 6 sessions.	(4) Patients will participate in six, 50-minute telephone-based sessions of the ACT intervention or education/support condition. Sessions will occur approximately 1 week from each other, with the first session occurring about 1 week following the baseline assessment. Sessions will be administered by a licensed therapist who will be trained and supervised by clinical psychologists.
Approximately 2 weeks, 3 months, and 6 months after the last intervention session. Assessments can be completed as early as 7 days prior to the target follow-up date or as late as 21 days following the target follow-up date.	(5) Patients will complete a follow-up assessment over the phone at approximately 2 weeks, 3 months, and 6 months post-intervention (see "interview procedures" below). Assessments will be administered by a trained research assistant or a trained doctoral student in clinical psychology who is blinded to the intervention arm.

5.0 Enrollment/Randomization

Following baseline assessments, patients (N = 250) will be randomly assigned to the ACT intervention or education/support condition using a stratified block randomization scheme to balance the groups by patient age (<65 vs. ≥65 years) and performance status (Eastern

Cooperative Oncology Group scores 0 or 1 vs. 2).[8, 9] We will stratify randomization by performance status because the decision to provide chemotherapy and other cancer treatments is often based on performance status.[10] Randomization will be performed by the IU Biostatistics Department. The study statistician will create the randomization procedure, and the PI will inform study therapists of their assigned patients. Other members of the study team will remain blind to participants' group assignment. All patients will be registered with the Indiana University Cancer Center Clinical Trials Office. Applicable regulatory documents must be completed and on file prior to registration of any patients.

6.0 Study Procedures

Recruitment Process

Electronic medical records for the study sites will be reviewed by a collaborating oncologist who is a co-investigator on this study or his or her authorized representative to identify patients who may be eligible for the study. Before sending a study introductory mailing to any potentially eligible patients, the project coordinator will discuss with the oncologist co-investigator if these potentially eligible patients may receive information about the study. An introductory letter signed by the patient's oncologist (the site PI, Dr. Goedde if a Community Health Network patient or the site PI, Dr. Addington if a Robert H. Lurie Comprehensive Cancer Center patient) and the PI will be sent to notify each potentially eligible person about the study (see Appendix A). The recruitment brochure (Appendix B), consent form, and authorization form will also be included in the initial mailing with the introductory letter. Any interested patients will be invited to call for more details. The letter also will have an "opt out" component; thus, patients who are not interested in the study may call the study office to indicate that they do not wish to be contacted further.

A research assistant will call all prospective participants who do not opt out within approximately 1 to 2 weeks after the letter is mailed. The research assistant will describe the study, review the consent form and authorization form, and ask if they would like to participate (see Appendix C for telephone script). During that initial call, interested patients will complete the eligibility screening assessment (Appendix D). The assessment will begin with the administration of the 7-item Fatigue Interference subscale of the FSI.[1, 2] Eligible patients will have a mean score ≥ 2.5, indicating moderate to severe fatigue interference. Then patients will complete the 1-item Patient Generated Subjective Global Assessment (PG-SGA; the patient-reported version of the Eastern Cooperative Oncology Group score).[8, 9] Those with a score above 2 will be excluded from the study. Next, patients will complete a validated 6-item cognitive screener.[7] Patients with 3 or more errors on this screener will be excluded from study participation. Those who are interested and eligible will provide verbal consent for study participation and verbal authorization to collect information from medical records. Verbal consent was chosen in place of written informed consent to minimize the number of documents that link the participant with the research and therefore reduce the risk of a breach of confidentiality. In addition, the entire study will be conducted via phone. Thus, we do not have the opportunity to obtain written consent during a face-to-face meeting with the patient. If a potential participant does not answer the phone, a brief voicemail will be left (see Appendix C for telephone script). We will speak with the potential participant up to 5 times within approximately 1 to 4 weeks after the first phone call or a longer period of time if the patient requests a call from staff at a later date. At least 2 weeks following the first voicemail message,

we will leave a second voicemail message if we have been unable to reach the prospective participant. Thus, we will leave a maximum of two voicemail messages.

The research assistant will review the entire consent form and allow the potential participant to ask any questions they may have prior to consenting. In addition, the authorization form will be reviewed with the potential participant. If the patient needs more time or wants more information, an appointment to call again to obtain verbal consent will be made. If requested, a new consent form and authorization form will be either mailed or emailed to them (based on their preference).

For patients who decline to participate in this study, we will ask if they would be willing to provide a reason for their decision. With the patient's permission, we will also document their age and race/ethnicity. Regarding patients who agree to complete the screening assessment and are found to be ineligible, we will also document their age and race/ethnicity with their permission. This information will be obtained solely for the purpose of determining potential sample selection biases. Should non-participants decline to answer these questions, we will discontinue all further contact with them.

Informed Consent Process

All potential participants will be informed as to their rights as volunteers in a research study and will provide informed consent for research participation. The key elements of the informed consent procedure which will be explained to prospective participants are: 1) the research status of the study; 2) the potential risks and the provisions for them; 3) the lack of guarantee of benefit from participation; 4) the voluntary nature of the study; 5) the lack of consequence to medical care of the decision to consent or refuse to participate; and 6) the freedom to withdraw from the study or to refuse to answer specific questions or to participate in any aspect of the study at any time. Consenting patients will have the option of providing the name and contact information for an emergency contact person who may be contacted in the event that the study team repeatedly cannot reach the participant (see Appendix O).

Interview Procedures

MBC patients (N = 250) who are eligible and provide informed consent will complete assessments at baseline and approximately 2 weeks, 3 months, and 6 months following the final intervention session (see Table 1 in section 5.0 above for allowable assessment windows). The baseline assessment takes about 35 minutes, and each follow-up assessment takes about 30 minutes. Assessments will include questions regarding demographics, medical history, primary and secondary outcomes, and potential mediating variables. Participants will be provided with copies of response options via email or postal mail to facilitate survey completion (see Appendix E). Each participant will receive $40 in Target gift cards via postal mail for each completed assessment (baseline and 2-week, 3-month, and 6-month follow-ups) for a possible total of $160 in gift cards for their time. Participants will not receive gift cards for the 6, 50-minute intervention sessions. There is no cost to study participants. Table 2 below outlines the assessment schedule at baseline and the three follow-ups.

Table 2. Measures

Domain	Measure	# Items	Baseline	2-week follow-up	3-month follow-up	6-month follow-up
Sociodemographics	Sociodemographics	7	X			
Medical comorbidity	Checklist of 9 conditions	9	X			
Functional status	Patient-reported ECOG	1	X	X	X	X
Cancer information (e.g., date of diagnosis, cancer treatments)	Chart review	n/a	X	X	X	X
Physical and mental healthcare use	Healthcare use interview	7 (6 at follow-up)	X	X	X	X
Medications	Medication interview	n/a	X	X	X	X
Primary outcome: fatigue interference	Fatigue interference subscale of FSI	7	X	X	X	X
Secondary outcomes:						
• Sleep interference	PROMIS short-form sleep-related impairment measure	8	X	X	X	X
• Engagement in daily activities	PROMIS short-form measure of ability to participate in social roles and activities	6	X	X	X	X
• QoL	FACT-G	27	X	X	X	X
Hypothesized mediator: psychological flexibility	Acceptance and Action Questionnaire-II	7	X	X	X	X
Exploratory mediators: mindfulness/acceptance and commitment/ behavior change	Cognitive and Affective Mindfulness Scale-Revised; Value Progress subscale of Valuing Questionnaire	15	X	X	X	X
Severity of symptoms: Fatigue severity, sleep disturbance, anxiety, depressive symptoms, pain, and cognitive symptoms	Fatigue severity and frequency items from FSI; PROMIS short-form measures of sleep disturbance, anxiety, depression, pain, hot flashes, and cognitive function	48	X	X	X	X

ECOG = Eastern Cooperative Oncology Group; FACT-G = Functional Assessment of Cancer Therapy-General; FSI = Fatigue Symptom Inventory; PROMIS = Patient Reported Outcomes Measurement Information System; QoL = quality of life.

Study Measures

A 5-minute screening assessment to determine eligibility will be conducted with MBC patients using the measures described below (see Appendix D).

Screening measures: Patients will first complete the 7-item Fatigue Interference subscale of the FSI.[1, 2] Eligible patients will have a mean score ≥ 2.5, indicating moderate to severe fatigue interference. Then patients will complete the 1-item Patient Generated Subjective Global Assessment (PG-SGA; the patient-reported version of the Eastern Cooperative Oncology Group score).[8, 9] Those with a score above 2 will be excluded from the study. Next, patients will complete a validated 6-item cognitive screener.[7] Patients with 3 or more errors on this screener will be excluded from study participation. All measures have well-established reliability and validity and have been studied in cancer populations.

Baseline and follow-up measures: Patients will complete a 35-minute baseline assessment and three, 30-minute follow-up assessments using the measures described below (see Appendices

F-G). Baseline and follow-up assessments will be audio-recorded so that the PI or a trained member of the study team may audit the assessments for adherence to the study protocol.

Demographic information. The following demographic information will be assessed at baseline: age, race/ethnicity, marital/partner status, number of household members and their relationship to the patient, education, income, and employment status. Rural status will be determined by classifying the patient's county of residence based on U.S. Census Bureau data.[11]

Medical factors and healthcare use. As in prior NIH-funded trials with cancer patients,[12, 13] we will assess medical comorbidities, functional status, cancer information (e.g., date of breast cancer diagnosis, cancer treatments received), and physical and mental healthcare use.[12, 14] Medical comorbidities will be assessed at baseline only; functional status, cancer information, and healthcare use data will be collected at baseline and the three follow-up assessments. Self-reported medical comorbidities will be assessed via a checklist of nine chronic health conditions. Functional status will be measured with the 1-item PG-SGA, a valid patient-reported version of the ECOG score.[8] Cancer information, such as time since diagnosis and treatments received, will be assessed via chart review. Additionally, seven items will assess physical and mental healthcare use, including outpatient and emergency room visits, use of complementary and alternative healthcare services, and (at baseline only) prior mindfulness training.[12, 14] Patients will also report their prescribed and over-the-counter medications.

Primary outcome: Fatigue interference. The primary outcome measure is the 7-item Fatigue Interference subscale of the FSI.[1, 2] Items are rated on 11-point scales (0=no interference; 10=extreme interference) that assess the extent to which fatigue in the past week interfered with general level of activity, ability to bathe and dress, normal work activity (including housework), ability to concentrate, relations with others, enjoyment of life, and mood. This measure has been extensively used with cancer patients with strong evidence of construct validity and internal consistency reliability.[15] In a review of fatigue measures for cancer patients, the FSI received the highest psychometric quality rating relative to other fatigue measures.[16] Cronbach's alphas have been excellent in prior studies (αs = .91-.95)[15] and our pilot research with MBC patients (αs = .92-.94).

Secondary outcomes. Two secondary outcomes will be assessed with Patient-Reported Outcomes Measurement Information System (PROMIS) measures, which have many advantages. PROMIS measures were developed using sophisticated measurement techniques and tested with over 21,000 people.[17-19] During measure development, cancer patients provided input to ensure their relevance for those with cancer.[20] The available short-forms have strong evidence of reliability and validity and showed good internal consistency and convergent and divergent validity in our pilot research with MBC patients.[21] Additionally, standardized T-scores facilitate comparisons with population norms. T-score distributions are standardized such that a score of 50 (SD = 10) represents the mean for the U.S. general population. U.S. cancer-specific reference values have been published for various PROMIS domains.[22] A non-PROMIS measure, the FSI,[1, 2] will be used to assess fatigue interference and severity, as the PROMIS short-form fatigue measures do not have subscales for these constructs. Finally, we will use another well-validated non-PROMIS measure, the FACT-G,[6] to assess QoL because many items on the FACT-G specifically refer to the patient's illness (e.g., "I am satisfied with how I am coping with my illness"), whereas PROMIS QoL items are not illness-specific.

1) Sleep interference will be assessed with the 8-item PROMIS sleep-related impairment measure.[3, 4] This measure assesses the perceived interference of sleep problems with activities, mood, and cognition.
2) Engagement in daily activities will be assessed with the 6-item PROMIS short-form measure of ability to participate in social roles and activities.[5] The items, which are reverse-coded,

measure difficulty engaging in social and recreational activities as well as usual work (including housework).

3) QoL will be measured with the 27-item FACT-G,[6] consisting of four subscales: Physical Well-Being, Social/Family Well-Being, Emotional Well-Being, and Functional Well-Being. An overall score is computed to represent general QoL.

Mediators. Psychological flexibility as measured by the 7-item Acceptance and Action Questionnaire-II (AAQ-II)[23] will be assessed as a hypothesized mediator of the intervention's effect on fatigue interference. Research has supported the reliability and validity of the AAQ-II for use with cancer patients.[24-26] The two core components of psychological flexibility (mindfulness/acceptance and commitment/behavior change) will also be assessed as exploratory mediators. First, mindfulness/acceptance will be measured by the 10-item Cognitive and Affective Mindfulness Scale-Revised (CAMS-R).[27] The scale provides a comprehensive assessment of mindfulness processes, including attention, present-focus, awareness, and acceptance/non-judgement. The measure showed strong evidence of reliability and validity in healthy samples,[27] and our team has an ongoing study to examine its psychometric properties in 200 MBC and other advanced cancer patients. Data collection is finished, and we are currently preparing the data for analyses. Second, commitment/behavior change will be measured by the 5-item Value Progress subscale of the Valuing Questionnaire.[28] This subscale assesses progress in living consistently with personal values and showed excellent reliability and validity in our pilot work with MBC patients.[21]

Measures of symptom severity. Fatigue severity and frequency will be measured with six items from the FSI,[1, 2] and sleep disturbance, cognitive symptoms, anxiety, and depressive symptoms will each be assessed with a 6-item PROMIS measure.[3, 4, 17, 22, 29, 30] Pain will be assessed with 3-item and 4-item PROMIS measures of severity and impact on functioning, respectively.[17] The 10-item Hot Flash Related Daily Interference Scale will be used to assess the impact of hot flashes on aspects of quality of life.[31]

ACT Intervention Procedures

Drs. Mosher and Johns developed the ACT manual, which was informed by literature on fatigue and related symptoms in MBC patients,[21, 32-34] the ACT model,[35, 36] previous ACT trials with cancer patients and other populations with chronic conditions,[24, 37-41] and Dr. Johns's extensive experience delivering ACT to cancer patients. In the pilot trial, the intervention addressed the interference of any symptoms with activities. We refined the manual for the current study to focus on fatigue interference because it is the most common concern of MBC patients,[42] and pilot findings were promising with respect to this outcome. The manual is found in Appendix H. Grounded in the ACT model,[35] the intervention is designed to increase psychological flexibility (i.e., full awareness of the present moment, including fatigue, while persisting in actions consistent with personal values) and thereby reduce fatigue interference.

Licensed therapists will deliver the intervention. Table 3 shows a summary of the ACT sessions. While the therapist will aim to hold sessions on a weekly basis for 6 weeks, participants will have up to 12 weeks to complete the 6 sessions. According to the ACT model,[43] psychological flexibility is cultivated through the practice of six psychological skills: acceptance, values, defusion, contact with the present moment, self as context, and committed action. These skills constitute mindfulness and acceptance processes and commitment and behavior change processes. Each session has a primary focus on one of the six psychological skills (see Table 3), although in-session exercises and home practice generally promote multiple skills simultaneously. During the first session, the patient's background and fatigue management strategies will be discussed, and the concept of mindfulness will be introduced. Participants will

complete a 3-item version of the Fatigue Symptom Inventory and a 4-item standardized assessment of anxiety and depressive symptoms at the beginning of each session (see Appendix I).[1, 29] Completion of this assessment will allow the therapist to monitor and respond to participants' fatigue and distress. Paper copies of the questionnaires will be provided to participants to facilitate survey completion. Across the six sessions, patients will practice mindfulness exercises, clarify their values, and set specific goals aligned with their values. Sessions will incorporate discussion of patients' cancer experience, as their energy level and personal goals will be discussed in the context of their current medical care, functional status, and emotional responses to cancer. Each session will include assessing and recording the patient's home practice of mindfulness and other skills and will end with a discussion of practice for the week ahead. Through skill practice, participants will learn new and more adaptive ways to respond to fatigue and other unwanted internal experiences (e.g., anxiety). Handouts summarizing the topics of each session (Appendix J) and a CD that our team developed to guide mindfulness practices will be mailed to participants. Participants will also have the option of receiving the mindfulness recordings via an emailed link from IU Box.

Table 3. ACT Session Description and Home Practice Assignments	
Topic (Targeted ACT model skill)	**Session and Home Practice (HP) Content**
Session 1: Introduction to Mindfulness (Acceptance)	• Introductions and overview of the intervention • Discuss patient's strategies for fatigue management, including control- vs. acceptance-based strategies and the workability of each in the context of coping with cancer • Introduce mindfulness and practice mindfulness (noticing sounds around her and her breathing) with therapist • HP1: Write a list of ways that fatigue has interfered with living a meaningful life; practice mindful breathing exercise daily; value-based goal
Session 2: Exploring What is Most Important to You (Values)	• Home practice review • Body scan mindfulness exercise and debriefing with reference to fatigue and the cancer experience • Clarify patient's values with birthday exercise and explore how patient might respond to fatigue in an adaptive, values-consistent manner • Patient rates consistency of actions with values using the Valued Living Questionnaire[44] • HP2: Engage in action step in line with values; practice body scan exercise daily and log what is noticed
Session 3: Decreasing Emotional Reactivity to Fatigue-related Thoughts and Emotions (Defusion)	• Practice "leaves on the stream" mindfulness with therapist • Home practice review • Discuss the patient's attempts to suppress the experience of fatigue and cancer-related thoughts and emotions (e.g., living with uncertainty) and the costs of these attempts in terms of reduced QoL • Explore the difference between "having" a thought and "buying" a thought • Further practice of mindfulness (noticing object or scene) with therapist • HP3: Write down two activities given up due to fatigue and any resulting emotions; practice "leaves on a stream" mindfulness exercise daily; value-based goal
Session 4: Mindful Awareness of Fatigue (Contact with the Present Moment)	• Practice mindfulness (noticing environment) with therapist • Home practice review • Practice mindful breathing • Introduce concept of willingness (i.e., flexibly making contact with the present moment, including fatigue) • HP4: Write down two activities that were enjoyed even while fatigued and resulting emotions; practice mindful breathing exercise daily; value-based goal
Session 5: Detaching from Fatigue (Self as Context or Perspective-Taking)	• Practice mindfulness (self-compassion exercise) with therapist • Home practice review • Discuss observing and detaching from fatigue and related thoughts and emotions to cultivate a transcendent sense of self from which to observe and accept changing experience • Discuss letting go and accepting things as they are • HP5: Goal setting and practice; daily mindfulness practice (patient's choice on CD)
Session 6: Taking Steps to Do What Matters to You (Committed Action)	• Practice mindfulness (brief body scan exercise) with therapist • Home practice review • Recap of skills and what patient learned • Goal setting around expanding patterns of values-consistent behavior after the study ends • Practice mindfulness (self-compassion exercise) with therapist • Termination and next steps in the study • HP6: Continue written goals

Education/Support Condition Procedures

The education/support control condition was tested in our pilot feasibility study.[45] The manual is found in Appendix K. Patients randomized to the education/support condition will discuss their concerns, including symptoms and other cancer-related stressors, with a therapist providing psychological support. The therapist will direct patients to resources for practical and health information and contact information for psychosocial services. Thus, this study tests whether ACT is superior to supportive listening and education regarding medical center and community resources, consistent with common interventions in clinical settings.

Licensed therapists will deliver the education/support intervention. Table 4 provides a summary of the sessions. While the therapist will aim to hold sessions on a weekly basis for 6 weeks, participants will have up to 12 weeks to complete the 6 sessions. Education/support participants will complete the same weekly fatigue and distress assessments as those in the ACT condition. Sessions will include an orientation to the patient's medical center and treatment team, education regarding common QoL concerns and symptoms experienced by cancer patients, and an overview of medical center and community resources for addressing these concerns. Therapists will also describe resources for addressing financial concerns and methods of evaluating health information available via the Internet and other modalities. Education/support participants will receive handouts summarizing the topics of each session and will be asked to review them as homework (Appendix L). ACT concepts will not be discussed in the education/support condition; thus, there is no overlap in intervention content between study conditions.

Table 4. Education/Support Session Description and Homework

Topic	Session and Homework (HW) Content
Session 1: Orientation to medical center and treatment team; Overview of QoL issues	• Overview of the upcoming sessions • Orientation to the medical center • Overview of components of QoL and discussion of physical QoL and symptoms • Discuss educational materials from the healthcare team • Overview of treatment team HW1: Review handouts on medical center information
Session 2: Resources for addressing social functioning	• Review common social challenges such as talking with children about cancer and employment issues • Contact information for resources to address social challenges HW2: Review handouts on contact information for resources to address social challenges
Session 3: Resources for addressing role and emotional functioning	• Tips on managing common household challenges when ill • Review common emotional responses to cancer, including anxiety and depressive symptoms, and cognitive changes following cancer treatment • Contact information for mental health services HW3: Review handouts on contact information for mental health services
Session 4: Resources for addressing financial concerns	• Review common financial concerns related to cancer and its treatment • Contact information for resources to address concerns HW4: Review handouts summarizing resources for addressing financial concerns
Session 5: Resources for evaluating health information	• Review methods of evaluating health information on the Internet and other modalities • Discuss resources for evaluating health information HW5: Review handouts summarizing resources for evaluating health information
Session 6: Review and further resources	• Review all topics discussed in prior sessions and available resources for addressing each topic area • Discuss websites for accessing cancer-related information HW6: Review handouts summarizing all resources

Training of Therapists and Treatment Fidelity

Training of therapists will involve didactics, live demonstrations, and role plays developed by the PI and her collaborators. All intervention sessions will be audio recorded, and the PI and Dr. Linda Brown (study consultant and licensed clinical psychologist) will randomly review 20% of recorded sessions to ensure fidelity and quality control. The PI will use therapist adherence checklists for the ACT and education/support conditions adapted from NIH-funded trials with

cancer patients (see Appendix M).[46] The PI and Dr. Brown will provide ongoing supervision of therapists. During individual supervision with therapists, which will occur approximately every 1-2 weeks, treatment adherence scores will be provided and treatment fidelity issues discussed. Role-plays will be conducted to correct deviations from study procedures.

7.0 Statistical Considerations

Design and data considerations. The primary and secondary outcomes in the proposed study are scaled continuously. For these outcomes, a linear mixed model using the SAS procedure MIXED will be employed.[47, 48] Because parameter estimation in MIXED employs full information maximum likelihood, all data the individual provides are included in the analysis even if some of the data are missing.

Preliminary analyses: Distributional issues. Univariate and descriptive analyses will be performed on all dependent variables, and if necessary, normalizing and/or variance stabilizing transformations will be sought in the family of power transformations and applied to the data before inferential analyses are undertaken. Missing data/subject attrition. We anticipate some missing data due to participant death, medical factors, and other reasons. For individuals who complete the first assessment but withdraw from the study, we will examine demographic, medical, and symptom factors that might be predictive of dropout using logistic regression. In the analyses for the primary and secondary objectives described below, all randomized participants will be included in intent-to-treat analyses,[49] as the aims are concerned with the impact of the intervention on outcomes regardless of study completion status. Second, for participants who miss assessments, it is possible that attrition may be related to the study condition to which they have been assigned. We plan to use the random effects pattern-mixture model proposed by Hedeker and Gibbons[50] to address missing data. Analyses of potential covariates. Because patients will be randomly assigned to the two study conditions, significant differences on the baseline values of all measured variables are not expected. T-tests and chi-square analyses will be performed to determine whether there are differences between the groups on potential baseline covariates (e.g., demographic and medical variables), and if there are differences these variables will be used as covariates in subsequent analyses.

Primary objective (2.1): To test the effect of telephone-based ACT on fatigue interference in MBC patients. A linear mixed-model repeated measures approach (SAS Proc-Mixed)[48] will be used to test the hypothesis (#1) that ACT will improve fatigue interference as compared to the education/support condition. The model will include the main effect of time (as categorical) and study group (ACT vs. education/support) and the time-by-study group interaction. A treatment effect will be evidenced by a significant interaction between time and study group. If the treatment effect is significant, follow-up tests will be conducted to examine group differences at each follow-up, controlling for the outcome at baseline.

Statistical power. Our sample size is calculated based on the estimated difference between study conditions (ACT vs. education/support) on the primary outcome of fatigue interference at 2 weeks post-intervention. In our pilot study, we found a moderate effect (d = -.30) of study condition on fatigue interference at 1 month post-intervention. It should be noted that only about half of the pilot sample had elevated fatigue interference at baseline (unlike the proposed study, the pilot study did not require all eligible patients to have clinically significant levels of fatigue interference); thus, the effect size is likely to be higher in the proposed study where the sample will have uniformly elevated fatigue interference at study entry. Indeed,

among patients with moderate to severe baseline fatigue interference in our pilot study, we found a strong effect (d = -.59) of study condition on fatigue interference at 1 month post-intervention. Thus, we conservatively estimate a medium effect size of d = -.40 at 2 weeks post-intervention. With a sample size of 198 patients at 2 weeks post-intervention (assuming 21% attrition), we will have 80% power (p = .05, two-tailed) to detect a Cohen's d of -.40 in a linear mixed model.[51] At the final, 6-month follow-up with a sample size of 163 (assuming 35% attrition), we will have 80% power (p = .05, two-tailed) to detect a Cohen's d of -.44.[51]

Secondary objective (2.2a): To test the effects of telephone-based ACT on secondary outcomes in MBC patients. Linear mixed models will be run in SAS Proc-Mixed[48] to test the hypothesis (#2) that ACT will improve sleep interference, engagement in daily activities, and QoL as compared to the education/support condition. Each model will include the main effect of time (as categorical) and study group and the time-by-study group interaction. A treatment effect will be evidenced by a significant interaction between time and study group. Probabilities for secondary outcomes will be Sidak adjusted for correlated multiple outcomes to control the familywise Type I error rate. If treatment effects are significant, follow-up tests will be conducted to examine group differences at each follow-up, controlling for the outcome at baseline.

Secondary objective (2.2b): To examine change in psychological flexibility as a mediator of ACT's effect on fatigue interference. The PROCESS macro for SAS developed by Andrew Hayes[52] will be used to test the hypothesis (#3) that increases in psychological flexibility will mediate the effect of ACT on fatigue interference. This analysis employs ordinary least squares regression. Bootstrapped confidence intervals will be computed for the indirect effect of study group on fatigue interference at 2 weeks post-intervention (via change in psychological flexibility over the same time period). The analysis will control for baseline levels of the mediator and outcome. We will also compute the indirect effects of study group on fatigue interference at 3 and 6 months post-intervention (via change in psychological flexibility at 2 weeks post-intervention). These analyses will also control for baseline levels of the mediator and outcome.

Exploratory objective (2.3): To explore changes in the two core aspects of psychological flexibility (i.e., mindfulness/acceptance and commitment/behavior change) as mediators of ACT's effect on fatigue interference. The PROCESS macro for SAS[52] will be used to explore the extent to which changes in mindfulness/acceptance and commitment/behavior change processes mediate the effect of ACT on fatigue interference. Both potential mediators will be entered into the same model. Bootstrapped confidence intervals will be computed for the indirect effect of study group on fatigue interference at 2 weeks post-intervention (via change in mindfulness/acceptance and commitment/behavior change processes over the same time period). The analysis will control for baseline levels of the mediators and outcome. We will also compute the indirect effects of study group on fatigue interference at 3 and 6 months post-intervention (via changes in mindfulness/acceptance and commitment/behavior change processes at 2 weeks post-intervention). These analyses will also control for baseline levels of the mediators and outcome.

Other exploratory analyses. To inform future research, we will explore the extent to which sociodemographics (e.g., age, education) and clinical characteristics (e.g., cancer treatments, baseline fatigue severity) moderate the effects of ACT on primary and secondary outcomes. For

these analyses, we will use linear mixed modeling at a two-sided significance level of 0.05. Preliminary findings or hypotheses generated from these moderation analyses will be further tested in a future trial.

8.0 References

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