Telephone Support for Advanced Gastrointestinal Cancer Patients and Caregivers

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1.0 Background & Rationale

Gastrointestinal (GI) cancers are among the most common cancers in the United States, and the majority are discovered at advanced stages.[1] Fatigue is a highly prevalent symptom in advanced GI cancer patients, with up to 68% reporting moderate to severe fatigue.[2, 3] Furthermore, when asked to rank symptoms and concerns, fatigue was the top concern for 62% of advanced colorectal cancer patients.[4] Fatigue often co-occurs with a number of other symptoms and substantially impacts daily activities and quality of life (QoL).[3, 5-8] Among advanced cancer patients, fatigue and related symptoms have been linked to prolonged hospitalizations and readmissions.[9] In our pilot work with advanced GI cancer patients (*N*=51), 67% reported moderate to severe difficulty initiating activities due to fatigue.

Treatments for fatigue have limited empirical support in advanced cancer,[10-12] leading to a critical unmet need for fatigue management in advanced GI cancer patients.[3, 4] A Cochrane meta-analysis evaluated randomized controlled trials (RCTs) of 18 pharmacologic treatments for fatigue in patients with advanced cancer and other late-stage chronic diseases.[10] Given the limitations of the evidence (e.g., small, heterogeneous samples) and minimal effect sizes in many trials, the authors did not make recommendations for fatigue treatment in these populations. Another Cochrane meta-analysis of 14 behavioral interventions for fatigue in advanced cancer, most of which were cognitive-behavioral and supportive-expressive therapies, drew similar conclusions.[12] Of note, only two intervention trials had a fatigue eligibility criterion.

As fatigue and related symptoms interfere with patients' daily functioning, family caregivers often assume a range of new responsibilities.[13-16] Our team found that among family caregivers of advanced GI cancer patients (*N*=50), 48% reported that they did not have enough time for themselves due to caregiving, and 76% reported moderate to severe stress due to balancing caregiving with other work and family obligations. Both of these reports and global caregiving burden were associated with reduced mental QoL, including symptoms of anxiety and depression (*r*s = -.30 to -.66). Similarly, in population-based research, cancer caregivers reported greater activity impairment and worse QoL than non-caregivers.[17]

Evidence-based interventions to reduce family caregiver burden in advanced cancer are lacking. Most behavioral interventions for cancer caregivers have been delivered to patient-caregiver dyads coping with early-stage breast or prostate cancer and did not have a symptom or distress criterion for study entry.[18-20] These interventions yielded small to medium effects on caregiver burden and QoL.[18-20] In addition, the limited RCTs with advanced cancer patient-caregiver dyads generally did not target those at greater risk for poor outcomes (e.g., those with high symptom interference with functioning or caregiving burden).[21-23] Thus, the generalizability of research findings to subgroups most in need of intervention has yet to be determined.

The significance of this trial is strengthened by the use of Acceptance and Commitment Therapy (ACT), a theory-driven behavioral approach,[24] to address fatigue interference with functioning in advanced GI cancer patients and caregiver burden. The goal of ACT is to increase psychological flexibility so that unwanted internal experiences (e.g., physical symptoms, feelings, thoughts) interfere less with meaningful activities.[24, 25] Psychological flexibility is defined as fully experiencing the present moment while

persisting in actions aligned with personal values.[24] ACT has a strong evidence base in chronic pain[26, 27] and mental health.[28, 29] A meta-analysis of 39 RCTs found that ACT was superior to control conditions for somatic symptoms (effect size [ES]=.58), anxiety/depression (ES=.37), and other mental disorders (ES=.92), representing a moderate to large treatment effect.[29] ACT has not been tested in caregivers of adults, with the exception of one RCT for dementia caregivers with high depressive symptoms.[30] In this trial, ACT led to similar or better mental health outcomes than cognitive-behavioral therapy (CBT).

ACT has also produced promising findings in pilot trials with cancer patients.[25, 31-33] In one trial, late-stage ovarian cancer patients were randomly assigned to 12 in-person sessions of ACT or 12 in-person sessions of CBT.[33] ACT participants showed large and significantly greater improvement in general distress (d = .89), global QoL (d = 1.35), anxiety (d = 1.26), and depressive symptoms (d = 1.69) than CBT participants over the intervention period. Notably, all attrition was due to death or beginning hospice; thus, ACT appeared to be feasible and acceptable to patients. Other pilot feasibility trials of ACT in cancer have also found positive changes in psychological outcomes.[25, 31] For example, Feros and colleagues tested a 9-session ACT intervention for distressed patients with various cancers.[25] General distress, mood, and global QoL significantly improved immediately post-intervention and three months later compared to baseline. Effect sizes for general distress and mood were large, and the effect size for global QoL was medium. These pilot data suggest that ACT warrants further study in cancer. Indeed, our team extended prior pilot studies by using telephone-based ACT to target fatigue interference and related outcomes in 47 MBC patients.[34] The intervention showed strong evidence of feasibility and promise with respect to fatigue and sleep interference relative to an education/support condition. Regarding feasibility, the majority (64%) of patients who could be reached via phone were screened for eligibility, and 100% of eligible patients consented. Additionally, retention was good with 83% of the entire sample completing the 8-week follow-up, and 79% completing the 12-week follow-up. Fatigue interference showed moderate reduction across time in the ACT group and minimal change in the education/support group; the between-group effect size was -.30 at 12 weeks. Furthermore, when examining the subsample (n = 24) with moderate to severe fatigue interference at baseline, the between-group effect size was -.59 at 12 weeks. ACT participants also showed decreased sleep interference at 12 weeks, with a between-group effect size of -.40 in the full sample and -.61 in the subsample with moderate to severe fatigue interference. Differences between study conditions were not significant; however, because it was a pilot study, we focused our analyses on effect sizes rather than statistical significance.

ACT can be widely disseminated to clinicians who care for advanced GI cancer patients and caregivers. Training in ACT is widely available and accessible to clinicians with various professional backgrounds, levels of education, and theoretical orientations. Furthermore, rather than being a fixed set of specific techniques, ACT draws from a broad range of traditional behavior therapy approaches as well as those outside the behavioral tradition (e.g., acceptance, mindfulness, identification of personal values).[24, 35] Thus, ACT is an adaptable approach that can be delivered as a stand-alone therapy and/or integrated into existing therapeutic approaches.

2.0 Study Objectives

Building on patient-focused ACT pilots in cancer,[25, 33, 34] this NCI-funded pilot trial tests a novel, *dyadic* telephone-based ACT program for addressing both fatigue interference (i.e., fatigue's negative impact on activities, mood, and cognition) in advanced GI cancer patients and family caregiver burden. In order to enhance translation to geographically dispersed individuals and those with high symptom burden or functional impairments, we will deliver the intervention via phone. Advanced GI cancer patients with moderate to severe fatigue interference and their primary family caregivers with significant caregiving burden (N=50 dyads) will be randomized to six weekly 50-minute telephone sessions of either (1) ACT or (2) education/support. ACT includes acceptance and mindfulness meditation exercises, identification of personal values, and engagement in activities consistent with these values. Examples of dyadic intervention components include joint mindfulness practices and having each participant describe the other person's strengths and resources for goal achievement. Feasibility will be examined via accrual, attrition, and adherence rates, and acceptability will be evaluated using a mixed methods approach (qualitative and quantitative). Outcomes will be assessed at baseline, 2 weeks post-intervention, and 3 months post-intervention. Findings will inform an R01 application to conduct a large-scale RCT of intervention efficacy. The study objectives are:

2.1 Primary Objective: To evaluate the feasibility and acceptability of delivering telephone-based ACT to advanced GI cancer patients and their caregivers.

2.2 Secondary Objective: To test the effects of telephone-based ACT on patient fatigue interference and caregiver burden (primary outcomes) as well as patient sleep interference and patient and caregiver engagement in daily activities, progress in value-based living, psychological flexibility, and QoL (secondary outcomes).
Hypothesis: ACT will lead to improved primary and secondary outcomes as compared to education/support.

2.3 Exploratory Objective:
To explore the effects of telephone-based ACT on patient and caregiver physical and mental health service use (tertiary outcomes).

3.0 Outcome Measures/Endpoints

All outcomes will be assessed at baseline, 2 weeks post-intervention, and 3 months post-intervention (see Table 1 of section 5.0 for complete timing details and assessment windows).

3.1 Primary Outcome Measures:

The primary outcome measure for patients is the 7-item Fatigue Interference subscale of the Fatigue Symptom Inventory (FSI).[36, 37] The primary outcome measure for caregivers is the 12-item short form of the Zarit Burden Interview,[38, 39] which evaluates caregiving burden (i.e., personal strain and role strain due to caregiving).

3.2 Secondary Outcome Measures:

(1) Patient sleep interference will be assessed with the 8-item Patient-Reported Outcomes Measurement Information System (PROMIS) sleep-related impairment measure.[40, 41] This measure assesses the perceived interference of sleep problems with activities, mood, and cognition.

(2) Patient and caregiver engagement in daily activities will be assessed with the 6-item PROMIS short-form measure of ability to participate in social roles and activities.[42] The items, which are reverse-coded, measure difficulty engaging in social and recreational activities as well as usual work (including housework).
(3) Patient and caregiver progress in value-based living will be assessed with the 5-item Value Progress subscale of the Valuing Questionnaire.[43]
(4) Patient and caregiver psychological flexibility will be evaluated with the 7-item Acceptance and Action Questionnaire-II (AAQ-II).[44]
(5) QoL. Patient QoL will be assessed with the 15-item McGill Quality of Life Questionnaire–Revised, which was designed for patients with life-threatening illnesses.[45] Caregiver QoL will be assessed with the 10-item PROMIS measure of global health.[46]

4.0 Eligibility Criteria

4.1 Patient Inclusion Criteria:

- Patient is at least 3 weeks post-diagnosis of unresectable stage III or stage IV gastrointestinal cancer (i.e., anal, colon, esophageal, gallbladder, liver, pancreatic, rectal, small intestine, or stomach cancer) and is receiving care at the Indiana University Simon Cancer Center or Eskenazi Health.
- Patient is at least 18 years of age.
- Patient has adequate English fluency for study participation.
- 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)[36, 37]
- Patient has an eligible, consenting family caregiver (see criteria below)

4.2 Patient Exclusion Criteria:

- Patient makes 3 or more errors on a validated 6-item cognitive screener[47] 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.[48]
- Patient is receiving hospice care at screening.
- Patient does not have working phone service.
- Patient has hearing impairment that precludes participation.

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

4.3 Caregiver Inclusion Criteria:

- Family caregiver identified by an unresectable stage III or stage IV gastrointestinal cancer patient who meets the eligibility criteria.

- Caregiver lives with the patient or has visited the patient in-person at least twice a week for the past month.
- Caregiver is at least 18 years of age.
- Caregiver has adequate English fluency for study participation.
- Caregiver is willing to participate in this study.
- Caregiver has moderate to severe caregiving burden, defined as a score ≥6 on the 6-item Zarit Burden Interview[39] or a T-score ≥60 (at least one standard deviation above the population mean) on the 4-item PROMIS anxiety or depression measures.[49]

4.4 Caregiver Exclusion Criteria:

- Caregiver exhibits significant psychiatric or cognitive impairment (dementia/delirium, retardation, active psychosis) that in the judgment of the investigators would preclude providing informed consent and study participation.
- Caregiver does not have working phone service.
- Caregiver has hearing impairment that precludes participation.
- Patient declines study participation.

5.0 Study Design

The study procedures are shown in **Table 1**. Advanced GI cancer patients and caregivers (*N* = 50 dyads) 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 and 3 months post-intervention within the timing windows outlined below.

Table 1

Timing	Procedure and person(s) responsible
At least 3 weeks after the patient's advanced GI cancer diagnosis	(1) The research assistant will contact potentially eligible patients, screen patients for eligibility, and obtain informed consent, which can be done verbally over the phone or face to face in the outpatient clinics at the IU Simon Cancer Center or Eskenazi Health (see "recruitment process" below). (2) The research assistant will contact potentially eligible caregivers, screen caregivers for eligibility, and obtain informed consent, which can be done verbally over the phone or face to face in the outpatient clinics at the IU Simon Cancer Center or Eskenazi Health (see "recruitment procedures" below). If the caregiver is not eligible or does not consent to participate, then the patient will be informed that s/he is not eligible for the study.

Target date = about 1 week after recruitment of the patient and caregiver. The baseline assessment can be completed up to 1 month after recruitment.	(3) Patients and caregivers who consent to participate will complete a 30- or 25-minute baseline assessment over the phone, respectively (see "interview procedures" below). The 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 and caregivers will participate in six, 50-minute telephone-based sessions of ACT or education/support. Sessions will be administered by licensed mental health professionals who are supervised by the PI and Dr. Johns who are clinical psychologists.
Target date = approximately 2 weeks after the last intervention session. Assessments can be completed as early as 7 days prior to this target follow-up date or as late as 14 days following the target follow-up date.	(5) Patients and caregivers will complete a 30-minute assessment over the phone (see "interview procedures" below). Assessments will be administered by a trained research assistant or a trained doctoral student in clinical psychology who are blinded to the intervention arm.
Target date = within 2 weeks of the 2-week post-intervention assessment. The qualitative interview can be completed as early as the same day as the 2-week follow-up or as late as 21 days after the 2-week follow-up.	(6) Patients and caregivers in the ACT condition will complete a 30-minute qualitative phone interview on intervention acceptability. The interview will be administered by a trained doctoral student in clinical psychology.
Target date = approximately 3 months after the last intervention session. Assessments can be completed as early as 7 days prior to this target follow-up date or as late as 21 days following the target follow-up date.	(7) Patients and caregivers will complete a 25- or 20-minute assessment over the phone, respectively. Assessments will be administered by a trained research assistant or a trained doctoral student in clinical psychology who are blinded to the intervention arm.

6.0 Enrollment/Randomization

Following baseline assessments, patient-caregiver dyads ($N = 50$) will be randomly assigned to the ACT intervention or education/support condition in a 1:1 ratio using a stratified block randomization scheme to balance the groups by patient performance status (Eastern Cooperative Oncology Group scores 0 or 1 vs. 2).[48, 50] We will stratify randomization by performance status because the decision to provide chemotherapy and other cancer treatments is often based on performance status.[51] Randomization will be performed using a SAS procedure routinely employed 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.

7.0 Study Procedures

Below, we first provide an overview of the recruitment and consent process followed by a description of the assessment and intervention procedures.

Recruitment Process
IU or Eskenazi Health medical records will be reviewed by collaborating oncologists who are co-investigators on this study or their authorized representatives to identify patients who may be eligible for the study (i.e., patients who are at least 3 weeks post-diagnosis of unresectable stage III or stage IV GI cancer) (see Screening form-Appendix S).

The oncologist or authorized representative will introduce the research assistant (RA) by name and ask the patient if the RA could speak with them about a research study. After being introduced by the patient's oncologist or authorized representative, the RA will meet with the patient before or after a clinic visit to describe the study as one examining telephone support programs for GI cancer patients and their family caregivers. They will meet in a private room and patients or caregivers may decline to speak with the RA. Patients will be asked if they have a family caregiver or friend who lives with them or has visited them at least twice per week for the past month. If multiple family caregivers are identified, patients will be asked if they would be willing to draw a circle and divide it based on the amount of caregiving provided by one or more family caregivers, indicating whom to designate as the primary caregiver. This approach has been used in other research on cancer caregiving.[52] Patients with an eligible caregiver will then be handed a print brochure (Appendix A), consent form, and authorization form that describe the study, including medical information that would be collected (see patient consent and authorization forms). After the research assistant provides an overview of the study and answers any questions, interested patients will complete a screening assessment. Conducting eligibility screenings for symptoms without obtaining patients' written informed consent has been standard practice at IU and other local medical centers for symptom management trials.

The evaluation will begin with the administration of a validated 6-item cognitive screener[47] by a trained research assistant (Appendix B). Patients with 3 or more errors on this screener will be excluded from study participation. 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).[48, 50] Those with a score above 2 will be excluded from the study. Next, patients will complete the 7-item Fatigue Interference subscale of the FSI.[36, 37] Eligible GI cancer patients will have a mean fatigue interference score $\geq$2.5. In our pilot work, 98% of metastatic breast cancer patients meeting this cutoff for fatigue interference at baseline also endorsed fatigue severity at least one-half standard deviation above the population mean. If a patient is ineligible for the study, the RA will tell them that they are not eligible, thank them for their time, and ask if they have any questions.

If the caregiver is present, s/he will also be provided with the study brochure, consent form, and authorization form. After the research assistant provides an overview of the study and answers any questions, interested caregivers will complete the 6-item Zarit Burden Interview[39] and the 4-item PROMIS anxiety and depression measures[49] (Appendix B). These will be completed on paper and responses will not be shared with the patient. Eligible caregivers will have a Zarit Burden Interview score of 6 or higher (an established cutpoint for advanced cancer caregivers) or a PROMIS anxiety or depression T-score of 60 or higher (at least one standard

deviation above the population mean). Caregivers who are eligible for the study and willing to participate may be consented face to face in the clinic. If the caregiver is not present, we will ask the patient for permission to send the study brochure, consent form, and authorization to the identified caregiver. If permission to contact the caregiver is denied, the patient and caregiver will be ineligible for the study. 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, gender, and race (Appendix S). Regarding ineligible patients, we will also document their age, gender, and race with their permission. This information will be obtained solely for the purpose of determining potential sample selection biases.

For potentially eligible caregivers who could not be approached in clinic, the research assistant will mail an introductory letter (see Appendix C), study brochure (Appendix A), informed consent form, authorization, and response option sheet for the phone screen (Appendix B). The letter will be signed by the principal investigator, Catherine Mosher, Ph.D. The letter will also introduce the research team and describe how the family caregiver will be contacted further about the study. Additionally, a phone number to contact the study staff with any questions or to express non-interest in study participation will be provided in the letter. All of this information should provide caregivers with the opportunity to think about questions they may have regarding the study. Within approximately one to two weeks of mailing the introductory letter, the research assistant will telephone caregivers to introduce the study and invite them to participate (see Appendix D for telephone script). If a potential participant does not answer the phone, a brief voicemail will be left (see Appendix D 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 caregiver 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 screen the caregiver for eligibility and obtain informed consent, a 10 to 15-minute conversation which can be done verbally over the phone or face to face in the outpatient clinics at the IU Simon Cancer Center or Eskenazi Health if the caregiver prefers. If the caregiver 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). Each person (patient or caregiver) has the option of providing their email address. In the event that we have made several unsuccessful phone call attempts to prospective participants, we will mail a letter to them indicating that they should contact the study staff if they are interested in discussing the study (see Appendix C). For caregivers who decline participation, we will ask if they would be willing to provide a reason for nonparticipation as well as their age, relationship to the patient, gender, and race (Appendix S). For caregivers who are ineligible, we will also document their age, relationship to the patient, gender, and race 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. If the caregiver declines study participation or is not eligible, then the patient will be informed that s/he is ineligible for the study.

While some patients will be approached in clinic as outlined above, other patients will be approached via a mailing and phone calls. 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 and the PI will be sent to notify each potentially eligible person about the study (see Appendix C). The recruitment brochure (Appendix A), 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 or email the research assistant 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 and authorization forms, and ask if they would like to participate (see Appendix D for telephone script). During that initial call, interested patients will complete the screening assessment described above (see Appendix B—screening questionnaires). The research assistant will read the items and response choices aloud and patients will select response options. 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 the 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 only once (see Appendix D for telephone script), and we will only speak with the potential research participant up to 5 times within approximately 1 to 4 weeks after the first phone call.

The research assistant will read the entire consent form verbatim 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).

During the consent process, patients will be asked if they have a family caregiver who lives with them or has visited them at least twice per week for the past month. We will ask the patient for permission to send the study brochure, consent form, and authorization to the identified caregiver. If permission to contact the caregiver is denied, the patient will be ineligible for the study. 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, gender, and race. 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.

If the family caregiver completes the eligibility screening and is not eligible for the study or declines to participate, then the research assistant will ask the patient if there is another family caregiver who meets the initial eligibility criteria (e.g., lives with them or has visited them for

twice a week during the past month). With the patient's permission, the same eligibility screening and consent process will be employed with the identified family caregiver. Up to 3 family caregivers per patient may be consecutively screened for eligibility. If none of the family caregivers are eligible and willing to participate, then the patient will be ineligible for study participation.

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 and caregivers 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 R for contact information sheets).

Inclusion of Women and Minorities

We will recruit advanced GI cancer patients and their primary family caregivers. According to American Cancer Society statistics,[1] 57% of GI cancers are expected to be diagnosed in men in 2019. Thus, we expect approximately 60% of our patient sample to be male. Evidence indicates that the majority of cancer patients' family caregivers are women;[53] indeed in our pilot work, 66% of caregivers of advanced GI cancer patients were women.[54] Thus, we expect approximately 65% of our caregiver sample to be female. No racial or ethnic group will be excluded from study participation. We will oversample racial and ethnic minorities to generate a sample representative of Indianapolis and surrounding areas. Eskenazi Health—one of our recruitment sites—sees a highly racially and ethnically diverse patient population. Based on recent data from the study sites, we anticipate that the final sample will be approximately 70% non-Hispanic White, 20% non-Hispanic Black or African American, 6% Hispanic, and 4% Asian or members of other racial/ethnic groups.

Interview Procedures

Advanced patients and caregivers ($N = 50$ dyads) who are eligible and provide informed consent will complete individual phone assessments at baseline and approximately 2 weeks and 3 months following the final intervention session (see Table 1 in section 5.0 above for allowable assessment windows). The baseline assessment takes about 30 minutes for patients and 25 minutes for caregivers. Each follow-up assessment takes about 25 minutes for patients and 20 minutes for caregivers. Interviewers will be blind to study condition. Assessments will include questions regarding demographics, medical history, and primary and secondary outcomes. Participants will be provided with copies of response options via email or postal mail to facilitate survey completion (see Appendix E). Patients and caregivers in the ACT condition will also be invited to complete a 30-minute individual qualitative interview about intervention acceptability within approximately two weeks of the 2-week follow-up assessment. Each participant will receive $40 in Target gift cards via postal mail for each completed assessment (baseline and 2-week and 3-month follow-ups) for a possible total of $120 in gift cards ($160 in gift cards for ACT participants only) for their time. There is no cost to study participants. If we cannot reach

a participant for an interview or phone session after several attempts, we will mail them a letter asking them to contact the study team (Appendix C). Table 2 below outlines the assessment schedule at baseline and the two follow-ups.

Table 2. Quantitative Measures

Domain	Measure	# Items	Baseline	2-week follow-up	3-month follow-up	Administered to Patients (P) or Caregivers (C)
Sociodemographics	Sociodemographics	7-8	X			P, C
Medical comorbidity	Checklist of 8-9 conditions	8-9	X			P, C
Functional status	Patient-reported ECOG	1	X	X	X	P
Cancer information (e.g., date of diagnosis, cancer treatments)	Chart review	n/a	X	X	X	N/A
Intervention acceptability	Intervention acceptability scale	6		X		P, C
Primary patient outcome: fatigue interference	Fatigue interference subscale of FSI	7	X	X	X	P
Primary caregiver outcome: caregiving burden	12-item short-form of Zarit Burden Interview	12	X	X	X	C
Secondary outcomes:						
• Sleep interference	PROMIS short-form sleep-related impairment measure	8	X	X	X	P
• Engagement in daily activities	PROMIS short-form measure of ability to participate in social roles and activities	6	X	X	X	P, C
• Progress in value-based living	Progress subscale of the Valuing Questionnaire	5	X	X	X	P, C
• Psychological flexibility	Acceptance and Action Questionnaire-II	7	X	X	X	P, C
• QoL	McGill Quality of Life Questionnaire–Revised (patients) or PROMIS global health measure (caregivers)	15 or 10	X	X	X	P, C
Tertiary outcomes:						
Physical and mental healthcare use	Healthcare use interview	7-8	X	X	X	P, C
Medications	Medication interview	n/a	X	X	X	P, C
Severity of symptoms:						
Fatigue severity, sleep disturbance, anxiety, depressive symptoms, pain, and cognitive symptoms	Fatigue severity and frequency items from the FSI; PROMIS short-form measures of sleep disturbance, anxiety, depression, pain, and cognitive function	30 or 37	X	X	X	P, C (except that pain is only assessed in patients)

ECOG = Eastern Cooperative Oncology Group; FSI = Fatigue Symptom Inventory; PROMIS = Patient-Reported Outcomes Measurement Information System; QoL = quality of life.

Study Measures

Advanced GI cancer patients and caregivers will each complete a 5-minute screening assessment to determine eligibility using the measures described below (see Appendix B).

Screening measures: Patients will first complete a validated 6-item cognitive screener.[47] Patients with 3 or more errors on this measure will be ineligible for this study. 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).[48, 50] Those with a score above 2 will be excluded from the study. Next, patients will complete the 7-item Fatigue Interference subscale of the FSI.[36, 37] Eligible patients will have a mean score ≥ 2.5, indicating moderate to severe fatigue interference. All measures have well-established reliability and validity and have been studied in cancer populations. Caregivers will complete the 6-item Zarit Burden Interview[39] and the 4-item PROMIS anxiety and depression measures.[49] Eligible caregivers will have a Zarit Burden Interview score of 6 or higher or a PROMIS anxiety or depression T-score of 60 or higher (at least one standard deviation above the population mean).

Baseline and follow-up measures: Patients and caregivers will complete a baseline assessment and two follow-up assessments using the measures described below (see Appendices F-I). The baseline assessment takes about 30 minutes for patients and 25 minutes for caregivers. Each follow-up assessment takes about 25 minutes for patients and 20 minutes for caregivers. All self-report measures have strong evidence of reliability and validity. PROMIS measures were tested with over 21,000 people, including cancer patients.[55-58] Validated non-PROMIS measures will be used for constructs that PROMIS measures do not currently assess (e.g., fatigue interference). Patients and caregivers in the ACT condition will also complete a 30-minute qualitative interview on intervention acceptability (see Appendix J). Baseline and follow-up assessments and qualitative interviews will be audio-recorded so that the PI or a trained member of the study team may audit them for adherence to the study protocol. Dr. Matthias, a qualitative methodologist, will randomly review at least 20% of qualitative interviews.

Demographic/medical factors. At baseline, patients and caregivers will report standard demographics (i.e., age, gender, race/ethnicity, marital status, education, income, employment status) and chronic medical conditions.[59, 60] Caregivers will also report their relationship to the patient. Patients' cancer information will be collected via chart review (Appendix S).

Feasibility and acceptability data. Feasibility will be assessed by accrual rates, attrition, and adherence. At the 2-week follow-up, acceptability will be assessed with helpfulness ratings on a scale from 1 (did not help at all) to 5 (extremely helpful) for number and length of sessions, topics, therapist, and telephone format.[54] The RA will be blind to study condition, as the questions apply to either condition. For ACT participants, acceptability will also be assessed within 2 weeks of the 2-week follow-up via a 30-minute qualitative phone interview on the perceived helpfulness and impact of ACT components (see Appendix J for detailed interview guide). Qualitative interviews will be conducted with patients and caregivers separately. A doctoral student in clinical psychology with qualitative interviewing experience will conduct the interviews.

Primary outcomes. For patients, fatigue interference will be assessed with the 7-item Fatigue Interference subscale of the FSI.[36, 37] Items assess the extent to which fatigue in the past week interfered with activities, such as bathing, dressing, and housework, ability to concentrate,

enjoyment of life, and mood. For caregivers, caregiver burden will be assessed with the 12-item short form of the Zarit Burden Interview,[38, 39] which evaluates personal strain and role strain due to caregiving.

Secondary outcomes. 1) Patient sleep interference will be assessed using the 8-item PROMIS sleep-related impairment measure,[40, 41] which evaluates the perceived interference of sleep problems with activities, mood, and cognition. 2) Patient and caregiver engagement in daily activities will be assessed with the 8-item PROMIS measure of ability to participate in social roles and activities.[42] The items, which are reverse-coded, measure difficulty engaging in social and recreational activities as well as usual work (including housework). 3) Patient and caregiver progress in value-based living will be measured by the 5-item Value Progress subscale of the Valuing Questionnaire.[43] This subscale assesses progress in living consistently with personal values. 4) Patient and caregiver psychological flexibility will be evaluated with the 7-item Acceptance and Action Questionnaire-II (AAQ-II).[44] 5) Patient QoL will be assessed with the 15-item McGill Quality of Life Questionnaire–Revised, which was designed for patients with life-threatening illnesses and evaluates physical, existential, and social well-being.[45] Caregiver QoL will be assessed with the 10-item PROMIS measure of global health, including physical, mental, and social well-being.[46]

Tertiary outcomes. Patients and caregivers will report their physical and mental healthcare use in five domains (e.g., ER visits, outpatient visits) in the past 3 months at baseline and over the study period.[59, 60] These reports of healthcare use were sensitive to change in an R01-funded cancer trial.[61] At all time points, participants will also report whether professionals referred them to support services and whether referred services were received.[52, 62] At all time points, participants will also report current medications using established methods from prior trials.[63, 64] We will compute the total number of medications at each time point, as this variable had strong predictive validity for both healthcare use and costs in older adults over a 1-year period.[65]

Measures of symptom severity. Symptom severity will be assessed to characterize the sample. For both patients and caregivers, fatigue severity and frequency will be measured with six items from the FSI,[36, 37] and sleep disturbance, cognitive symptoms, anxiety, and depressive symptoms will each be assessed with an 6-item PROMIS measure.[40, 41, 49, 57, 58, 66] Patients will also complete 3-item and 4-item PROMIS measures of pain severity and impact on functioning, respectively.[58]

ACT Intervention Procedures

Drs. Mosher and Johns developed the ACT manual (see Table 3 and Appendix K), which was informed by literature on the experiences of advanced GI cancer patients and caregivers,[2, 3, 15, 67, 68] the ACT model,[24, 35] previous ACT trials with cancer patients and other populations with physical and mental health conditions,[25, 26, 29, 31, 33, 34] and Dr. Johns's extensive experience delivering ACT to cancer patients and caregivers. A licensed therapist will deliver the intervention. 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. Patients and caregivers will complete sessions 1 and 4-6 together via speakerphone. Sessions 2 and 3 will be delivered to patients and caregivers separately. Holding both dyadic and individual sessions will allow the therapist to meet the shared and unique needs of patients and caregivers. We adapted ACT to the dyad by incorporating joint mindfulness practices and leveraging the relationship during discussions. For example, participants will discuss moments of emotional connection with each

other as instances of mindfulness and provide encouragement to the other person during goal setting. Individual sessions with patients and caregivers will include exploration of personal values. In addition, the workability of attempts to avoid fatigue (if a patient) or unwanted thoughts and feelings about caregiving (if a caregiver) will be discussed. Thus, the focus of individual sessions is shifting from avoidant responses to the pursuit of value-based action despite fatigue or perceived caregiving burden.

According to the ACT model, psychological flexibility is established through the practice of six skills.[69] 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 and caregiver's background and coping strategies will be discussed, and the concept of mindfulness will be introduced. Patients will complete a 3-item version of the FSI, and patients and caregivers will complete a 4-item standardized assessment of anxiety and depressive symptoms at the beginning of each session (see Appendix L).[36, 49] 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, participants will practice various mindfulness exercises, clarify their values, and set specific goals aligned with their values. Sessions will also include discussion of patients' and caregivers' experiences coping with cancer. Each session will include assessing and recording participants' home practice of mindfulness, value-based action, and other skills and will end with a discussion of practice for the week ahead. Through skill practice, participants will learn new, adaptive ways to respond to unwanted internal experiences (e.g., fatigue, distress). Handouts summarizing the topics of each session (Appendix M) and a CD that our team developed to guide mindfulness practices will be mailed to participants along with a box of raisins for a mindful eating exercise. Participants will also have the option of receiving the mindfulness recordings via an emailed link from IU Box.

Table 3. Summary of ACT Intervention Manual	
Topic (*targeted ACT model skill*)	**Session and Home Practice (HP) Content**
Session 1 (dyadic) Introduction to Mindfulness (*Acceptance*)	• Introductions and overview of the intervention • Discuss control- vs. acceptance-based strategies for patient fatigue management and caregiver coping with emotions about responsibilities • Introduce and practice mindfulness (body scan) with therapist HP1: Complete questionnaire on consistency of actions with personal values;[70] practice mindfulness (body scan) daily and one value-based goal
Session 2 (individual) Exploring What is Most Important to You (*Values*)	• Practice mindfulness (awareness of the breath) with therapist • Clarify personal values with birthday exercise and explore how person might choose to respond to fatigue (if patient) or thoughts/emotions about tasks (if caregiver) in an adaptive and values-consistent manner HP2: Engage in actions in line with values; practice mindfulness (awareness of the breath) daily and log what is noticed
Session 3 (individual) Facing Internal Experiences (*Defusion*)	• Practice mindfulness ("leaves on the stream") with therapist • Explore workability of patient/caregiver attempts to avoid or suppress unwanted internal experiences (e.g., fatigue, thoughts/emotions about caregiving) and how these attempts lead to actions not aligned with values and reduced QoL • Practice mindfulness (self-compassion exercise) with therapist HP3: Write down a valued activity given up due to fatigue (if patient) or thoughts/feelings about caregiving and resulting emotions; also write down a valued activity that was pursued despite fatigue or caregiving and resulting emotions; practice mindfulness ("leaves on a stream") daily and one value-based goal
Session 4 (dyadic) Mindful Awareness (*Contact with the Present Moment*)	• Practice mindfulness (mindful eating of raisin) with therapist • Experiential exercise to support patients and caregivers in flexibly choosing their focus in the present moment and debriefing with reference to fatigue and cancer caregiving • Introduce concept of willingness (i.e., flexibly making contact with the present moment, including fatigue and thoughts/feelings about tasks) HP4: Do two routine activities with greater awareness; practice mindfulness (Tracks 1, 2, 3, or 4 on CD) daily
Session 5 (dyadic) Detaching from Internal Experiences (*Self as Context*)	• Practice mindfulness (3-step self-compassion practice) with therapist • Exercises to promote observing and detaching from fatigue and emotions about cancer or caregiving to cultivate a transcendent sense of self from which to observe and accept changing experience HP5: Goal setting; practice value-based goal; daily mindfulness practice (person's choice on CD)
Session 6 (dyadic) Taking Steps to Do What Matters to You (*Committed Action*)	• Practice mindfulness (brief body scan exercise) with therapist • Recap of skills and what patient and caregiver learned • Goal setting around expanding values-consistent behavior into future • Termination and next steps in the study HP6: Continue written goals

Education/Support Condition Procedures

Dyads in the education/support arm will be directed 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 on medical center and community resources, consistent with common interventions in clinical settings. The duration of sessions and number and order of dyadic vs. individual sessions will be identical to the ACT condition. A similar comparator was used in our ACT pilot trial with metastatic breast cancer patients,[34] and similar comparison groups have been used in studies with primarily advanced cancer patient-caregiver dyads.[71, 72] A licensed therapist will deliver the education/support intervention. Table 4 provides a summary of the topics for each education/support session, and the manual is found in Appendix N. 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. Participants will receive handouts on session topics and will be asked to review them as homework (Appendix O). ACT concepts will not be discussed.

Table 4. Summary of Education/Support Manual

Topic	Session and Homework (HW) Content
Session 1 (dyadic): Orientation to medical center and treatment team; QoL	• Overview of sessions & orientation to the medical center • Overview of QoL and discussion of physical QoL • Discussion of educational materials received from the healthcare team • Overview of treatment team HW1: Review handouts on medical center information
Session 2 (individual): Resources that address social functioning	• Review common challenges in social functioning such as talking with children and employment issues • Contact info for resources to address social challenges HW2: Review handouts on resources to address social functioning
Session 3 (individual): Resources that address role and emotional functioning	• Review common changes in activities • General tips on managing the household • Review common emotional responses to cancer and cognitive changes following cancer treatment • Contact information for mental health services HW3: Review handouts on mental health resources
Session 4 (dyadic): Resources for financial concerns	• Review common financial concerns related to cancer and its treatment • Contact information for resources to address concerns HW4: Review handouts on resources for addressing financial concerns
Session 5 (dyadic): Resources for evaluating health info	• Review methods of evaluating health information on the Internet and other modalities • Discuss resources for evaluating health information HW5: Review handouts on resources for evaluating health information
Session 6 (dyadic): Review and other resources	• Review all topics discussed in prior sessions and available resources for addressing each topic area • Discuss websites for accessing cancer-related info 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. Shelley Johns (study co-investigator 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 P).[73] The PI and Dr. Johns 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.

Protection of Human Subjects

The protocol has several measures to monitor for, respond to, or minimize potential distress or anxiety detailed below. However, it is important to place the risk of distress in perspective. Based on survey evaluations by cancer patients and caregivers enrolled in other psychosocial studies,[52, 62] participants should not find the questions or the time requirements of the study to be burdensome. In fact, a large proportion of individuals who have participated in similar studies have commented that they felt that they have benefited from sharing their experiences and taking part in interventions. Thus, the risk of distress is modest and the safeguards detailed below should be adequate.

- Study team members will clearly acknowledge the voluntary nature of participation and individuals will have the ability to decline further contact from study personnel (i.e., to opt out).
- The research assistant, qualitative interviewer, and study therapists will receive training from Dr. Mosher, a clinical psychologist with extensive clinical and research experience with medical populations. This training will include ways to identify and respond to signs of distress.
- Participants will be fully informed about the study during the informed consent process and instructed to decline to answer any question or to discuss any issues they find troubling. If the interviewer feels that the participant is becoming anxious or fearful over a question, the interviewer will move on to the next question and document the reasoning.
- We will provide a letter with the principal investigator's and research assistant's names and phone numbers and instructions to call with questions or concerns.
- If a participant expresses significant distress (e.g., suicidal ideation) at any point during the study, Drs. Mosher or Johns (both clinical psychologists) will assess the participant and make an appropriate referral for clinical care if needed. In addition, for distressed patients, Dr. Mosher or another study team member will contact the referring oncologist to inform them of the patient's high level of distress. Patients will also be encouraged to contact the healthcare team if they experience moderate to severe symptoms.

Suicidality Risk Protocol

If a participant expresses suicidal ideation, our research team will use an evidence-based algorithm that was developed in 4 earlier depression effectiveness trials in medical patients[74-77] and was tested in two recent trials in general medical (SCAMP trial)[78] and cancer (INCPAD trial)[60] patients. Evidence supports the utility of this algorithm (Appendix Q).[79] By this algorithm, participants are classified as minimal, lower, or higher risk. Participants with higher risk of suicide according to this algorithm will be considered for emergency detention. The latter constitute <2% of participants enrolled in depression trials, and we have a protocol for expedited evaluation by a clinical psychologist for the rare participant in the higher risk group, also tested in the SCAMP and INCPAD trials. All research personnel will be trained by the PI in this protocol. Specifically, after asking follow-up questions (see Appendix Q), Dr. Mosher or Dr. Johns (both clinical psychologists) will review the information the same day to determine the

appropriate course of action. If they believe that the participant is in immediate danger of harm, they will report it, potentially to authorities including the police. If the participant is not receiving mental health services, then they will be referred to mental health services at a location convenient to them.

8.0 Reportable Events

All contact with the participant will be documented beginning at the consent process through completion of the study. All documentation will be reviewed regularly. Any events that might indicate increased participant distress or anxiety will be promptly brought to the attention of the PI and reported to the IRB and DSMC per reporting guidelines listed below. We will promptly report to the IRB any instances of consent withdrawal due to distress or anxiety. The IRB will be informed at least annually of our data and safety monitoring, summary of participant status, and any changes in the risk of the study.

Reporting to the IRB:
1. Unanticipated problems involving risks to subjects or others will be reported **promptly** to the IRB if they:

- are unexpected;
- are related or possibly related to participation in the research; and
- suggest that the research places subjects or others at a greater risk of harm than was previously known or recognized.

If the serious adverse event does not meet all three (3) criteria listed above, the event does not have to be promptly reported to the Indiana University IRB. However, it should be reported at the time of continuing review.

2. **Prompt** reporting of unanticipated problems to the IRB is defined as within 5 days from becoming aware of the event. AEs will be monitored from the time of consent until the person's participation in the study has ended.

Reporting to the IUSCC Data Safety Monitoring Committee:
Regardless of study sponsorship, the study team must enter all initial and follow-up SAE, expedited, and noncompliance reports into OnCore® for review by the DSMC chair and/or coordinator. Expedited reports may include IRB Prompt Report Forms and additional SAE forms as required by the sponsor. When follow-up information is received, a follow-up report should also be created in OnCore®. This DSMC reporting requirement is **in addition to any other** regulatory bodies to be notified (i.e. IRB, etc.). The DSMC chair and/or coordinator will review all SAE, expedited, and noncompliance reports monthly.

9.0 Data Safety Monitoring

This study will be conducted in accordance with the IU Simon Cancer Center Institutional DSMP for **Low Risk Trials.**

Investigators will conduct continuous review of data and subject safety. **Quarterly review meetings** for low risk trials are required and will include the principal investigator, clinical research specialist and/or research nurse (other members per principal investigator's

discretion). **Quarterly** meeting summaries should include review of data, the number of subjects, significant toxicities as described in the protocol, and responses observed. Study teams should maintain meeting minutes and attendance for submission to the DSMC upon request.

Data and Safety Monitoring Committee
The IUSCC Data and Safety Monitoring Committee (DSMC) is responsible for oversight of subject safety, regulatory compliance, and data integrity for this trial. The DSMC will review this study annually to review overall trial progress, toxicity, compliance, data integrity, and accrual per the Institutional DSMP.

Furthermore, the DSMC conducts an administrative review of serious adverse events (SAEs), deviations, reportable events, and any other outstanding business. Major issues may require further DSMC review or action.

At any time during the conduct of the trial, if it is the opinion of the investigators that the risks (or benefits) to the subject warrant early closure of the study, the DSMC Chair and Compliance Officer must be notified within 1 business day via email, and the IRB must be notified within 5 business days. Alternatively, the DSMC may initiate suspension or early closure of the study based on its review.

Study Auditing and Monitoring
All trials conducted at the IUSCC are subject to auditing and/or monitoring per the Institutional DSMP. Reports will be reviewed by the full DSMC at the time of study review.

Data Management/Oncore Reporting Requirements
The DSMC reviews data and study progress directly from Oncore; therefore, timely data entry and status updates are vital. Study data must be entered within Oncore promptly, no later than one week from study visit occurrence. Subject status in Oncore will be updated in real time, as this may affect overall trial enrollment status. Global SAEs and deviations will be reviewed on a monthly basis by the DSMC Chair directly from Oncore.

Study Accrual Oversight
Accrual data will be entered into the IU Simon Cancer Center OnCore system. The Protocol Progress Committee (PPC) reviews study accrual twice per year, while the PPC coordinator reviews accrual quarterly.

Oncore Safety Reporting
In addition to protocol- and regulatory-required safety reporting, all serious adverse events (SAEs) will be captured in the Oncore system within 1 business day of notification. Initial SAE reporting will include as much detail as available, with follow-up to provide complete information. Attributions will be assessed to study drugs, procedures, study disease, and other alternate etiology.

Protocol Deviation Reporting
Protocol deviations will be entered into OnCore within 5 days of discovery and reviewed by the DSMC Chair on a monthly basis. Findings will be reported to the full DSMC at the time of study review.

10.0 Study Withdrawal/Discontinuation

Criteria for removal from the study are as follows:

- Observed severe cognitive impairment that renders continued participation in the study impossible, such as confusion or impaired ability to read or to provide accurate answers to the interviewer.
- The patient consents to participate in the study, but their family caregiver declines study participation or is not eligible for this study. The patient would no longer be eligible to participate in this study, as we are interested in examining data from patient-caregiver dyads.
- If the patient or caregiver is no longer able to participate in this study due to death or medical factors or decides to stop participation, then the other member of the dyad (patient or caregiver) will no longer be eligible to participate in this study.
- The participant expresses significant distress related to completion of the study (the PI will refer the participant to clinical services if needed).
- The participant provides verbal or written notification that she has decided to discontinue study participation.
- The participant does not follow the study rules (e.g., repeatedly does not answer the phone to complete a scheduled interview).
- Any other reason for which the principal investigator believes the participant should be withdrawn.

11.0 Statistical Considerations

Aim 1. Feasibility and acceptability will be evaluated via descriptive statistics for accrual, attrition, and adherence as well as Likert-scale items assessing intervention helpfulness. We will judge this trial as feasible if: 1) ≥60% of screened eligible dyads enroll in the study;[21] and 2) ≥70% of enrolled dyads complete 5-6 intervention sessions and all assessments. We will judge this trial as acceptable if ≥70% of dyads rate ACT as moderately to extremely helpful (i.e., an average score ≥4 on 1 to 5 Likert scale items).

To analyze qualitative data on ACT's acceptability, we will use an immersion/crystallization approach.[80] Research questions guiding the analysis pertain to the perceived helpfulness of ACT components and their impact on functioning and well-being. Interviews will first be transcribed by a trained research assistant. Analysis of the interview data will consist of two phases: open and focused coding.[80, 81] In the open coding phase, the analysts (Drs. Mosher, Matthias, and a Ph.D. student in clinical psychology) will independently label each line of data to reflect meanings or themes emerging from the text. This is done iteratively, combining, adding, or eliminating themes, until analysts agree on a set of emergent thematic categories (codes). In focused coding, codes derived in open coding are independently applied to all transcripts. Special attention will be paid to negative cases (i.e., data that may call initial observations or interpretations into question).[82] Transcripts will be divided evenly among analysts, with every fourth transcript coded in common to maintain consistency in coding over time. Analysts will meet bi-weekly to compare commonly-coded transcripts. Discrepancies will be resolved by consensus. Atlas-ti software will facilitate coding, and qualitative results will inform intervention refinement.

Aim 2. Given that this is a pilot study, our data analytic approach for Aim #2 will be to derive effect size estimates rather than test for statistical significance. A linear mixed-model repeated measures approach (SAS Proc-Mixed) will be used to examine ACT's effects on primary and secondary outcomes. For outcome measures that only patients or caregivers complete (e.g., patient fatigue interference or caregiver burden), models will include main effects of time (as categorical) and study group and the time-by-study group interaction. Treatment effects will be evidenced by the interaction between time and study group (i.e., group mean differences after the intervention but no such differences at baseline). Models will include random intercepts to account for nonindependence of individuals' scores across time. For outcomes reported by patients and caregivers (e.g., psychological flexibility), multilevel modeling for dyadic data will be used.[83, 84] Models will include the main effects of time, study group, and social role (patient vs. caregiver) as well as all two and three-way interactions between these variables. The time x study group x role interaction will estimate the degree to which treatment effects are different for patients and caregivers. Dyadic models will include random intercepts for patients and caregivers, as well as the covariance between the intercepts to account for nonindependence across time and across partners.

Aim 3. To conduct data analyses for Aim #3, we will use logistic and Poisson regression models to explore the effects of ACT on patient and caregiver physical and mental health service use (e.g., number of patient ER visits, patient and caregiver use of counseling and/or psychiatric medication). Logistic and Poisson regression analyses are appropriate for binary and count outcome data, respectively. Analyses will examine study condition as a predictor of health service use over the entire study period, controlling for baseline service use. Support service referrals will be a covariate in analyses of mental health service use.

Statistical power. Although our analyses focus on effect sizes rather than statistical significance, we calculated power for comparing primary outcomes (patient fatigue interference and caregiver burden) between study groups. With a sample size of 34 patients and 34 caregivers at 2 weeks post-intervention (assuming 15% attrition), we will have 80% power (p=.05, two-tailed) to detect a large intervention effect (d=.99) on either primary outcome in a linear mixed model.[85] ACT had large effects on distress and QoL outcomes in late-stage ovarian cancer patients (ds=.89-1.69) compared to CBT[33] and a medium effect (d=-.59) on fatigue interference compared to education/support in metastatic breast cancer patients with moderate-severe baseline fatigue interference.[34]

Missing data. All data will be assessed for missingness and multiple imputation with 50 imputed samples will be used.[86] We will also compare participants and those who decline participation or withdraw on demographic and medical factors using t-tests and Chi-square analyses. Further, we will carefully track study participation and try to understand the reasons for dropout and missing data wherever possible. Identifying potential dropout and missing data mechanisms will allow us to incorporate those factors as auxiliary variables for multiple imputation as well as full information maximum likelihood estimation method assuming Missing at Random in our future Phase II trial.

Potential covariates. T-tests and chi-square analyses will be performed to identify any group differences in potential baseline covariates (e.g., demographic and medical variables), and if there are differences these variables will be used as covariates.

12.0 Statistical Data Management

Primary data will be collected via phone interviews and stored electronically in passphrase protected files on the secure Psychology network drive accessed through an encrypted computer. Only IRB-approved members of the research team will have access to study files. The storage location will be backed up automatically every day. Paper files will be stored in a locked filing cabinet in a locked room in the PI's laboratory. Other data sources include data from medical records that will be stored in separate passphrase protected electronic files and merged with the primary data as needed. Quality assurance steps will include built in range checks. The following quality control methods will be used: 1) single data entry with two independent checks of the accuracy of every data point; and 2) discussion of any data entry questions with the PI.

13.0 Privacy/Confidentiality Issues

To protect against loss of confidentiality and anonymity, participant data will be identified only by a unique identification number assigned to each participant upon enrollment. Except for this unique identification number, no other identifying information will appear on the interview documents collected during the study. The master file linking the participant names with their identification numbers will be stored in a passphrase protected electronic file on a secure network drive. Unless required by law, no identifying information will be shared with individuals or organizations not affiliated with the study. Regarding individuals who are not eligible for this study or decline study participation, their screening information will be stored separately from identifying information (e.g., names) and will be kept for auditing purposes for 3 months before being destroyed.

Data will be housed on the secure departmental server in Excel and SPSS as well as in Oncore. The OnCore® database is a comprehensive, web-based, Clinical Trial Management System (CTMS) which utilizes an Oracle database. OnCore® was developed by Forte Research Systems, Inc. and is used by the IUSCC Clinical Trials Office and supported by the Indiana Clinical and Translational Sciences Institute (CTSI). OnCore® properly used is compliant with Title 21 CFR Part 11. OnCore® provides users secure access with unique IDs/passwords and restricts access by assigned roles, from any location, to record, manage, and report on data associated with the operation and conduct of clinical trials.

Furthermore, all study materials and data will be kept in locked file cabinets in a locked office and in passphrase protected electronic files on the secure departmental server. Only project members will have access to the files via encrypted computers. Participant identifiers will be removed from qualitative interview transcripts. Finally, once data collection has concluded, the master file linking participant names with identification numbers will be destroyed.

14.0 Follow-up and Record Retention

Data collection is expected to take place for up to 2 years. Data will be retained for a minimum of 7 years in accordance with Indiana State law. Data will be destroyed in the following manner: (1) paper will be shredded; (2) computer files will be deleted; and (3) audio-recording files will be deleted.

15.0 References

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16.0 Appendices

Appendix A: Study brochure

Appendix B: Screening questionnaires for patients and caregivers

Appendix C: Study letters

Appendix D: Phone script for consenting patients and caregivers

Appendix E: Response option sheets for patients and caregivers

Appendix F: Baseline interview for patients

Appendix G: Baseline interview for caregivers

Appendix H: Follow-up interviews for patients

Appendix I: Follow-up interviews for caregivers

Appendix J: Qualitative interview protocol for patients and caregivers in the ACT condition

Appendix K: Manual for ACT intervention condition

Appendix L: Patient and caregiver questionnaires for ACT and education/support sessions

Appendix M: Handouts for ACT intervention condition

Appendix N: Manual for education/support condition

Appendix O: Handouts for education/support condition for patients and caregivers

Appendix P: Therapist adherence checklists

Appendix Q: Suicide screening instrument

Appendix R: Patient and caregiver contact information sheets

Appendix S: Screening Form, refuser information, and medical data collection sheets