Acceptance and Commitment Therapy for Chronic Pain in Cancer Survivors

Protocol Number:	18-1102
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STATEMENT OF COMPLIANCE

This is an investigator-initiated study. The principal investigator (PI), Jamie L. Studts, PhD, is conducting the study and acting as the sponsor. As the sponsor-investigator, both the legal/ethical obligations of a PI and those of a sponsor will be followed.

The trial will be carried out in accordance with Good Clinical Practice (GCP) as required by applicable United States (US) laws and applications, including but not limited to United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46,)

The PI will assure that no changes to the protocol will take place without documented approval from the Institutional Review Board (IRB). All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Sponsor-Lead Principal Investigator: Jamie L. Studts, PhD
Print/Type Name

Signed: _____ **Date:** _____

LIST OF ABBREVIATIONS

ACRONYM	DESCRIPTION
ACT	Acceptance and Commitment Therapy
CAAQ	Cancer Acceptance and Action Questionnaire
CPAQ	Chronic Pain Acceptance Questionnaire
CRP	Cancer Related Pain
EHR	Electronic Health Record
IIT	Investigator-Initiated Trial
IRT	Item Response Theory
PROMIS	Patient-Reported Outcome Measurement Information System
SF-36	Medical Outcomes Study 36-Item Short Form Health Survey
TAU	Treatment as Usual

PROTOCOL SUMMARY / SYNOPSIS

Protocol Title: *Acceptance and Commitment Therapy for Chronic Pain in Cancer Survivors*

Objectives:

- ***Primary Objective:***
  To evaluate the feasibility, acceptability, and fidelity of implementing of an 8-week, group-based, Acceptance and Commitment Therapy (ACT) intervention for chronic pain management in cancer survivors who have completed active treatment.

- ***Secondary Objectives:***
  To evaluate preliminary clinical efficacy of an 8-week, group-based, ACT intervention for chronic pain management in cancer survivors who have completed active treatment.

Endpoint:

- ***Primary Endpoint:***
  The primary implementation outcomes are feasibility, acceptability, and fidelity. Following completion of the intervention, semi-structured qualitative interviews with intervention group members will be used to assess participant acceptability of the ACT intervention content, complexity and credibility, as well as patients' perspectives on intervention delivery. Additionally, weekly rating forms using Likert scales to collect quantitative data will be used to assess acceptability of content for each individual group therapy session. Feasibility will be evaluated through the collection of participant enrollment and adherence data throughout the intervention period and follow-up. Fidelity of the treatment will be measured through observation and the use of standardized checklist of core intervention components

- ***Secondary Endpoints:***
  The secondary clinical efficacy outcomes are physical and emotional functioning as measured by the SF-36. Implementation outcomes will include acceptability, feasibility, and fidelity..

- ***Tertiary/exploratory:***
  Tertiary/exploratory outcomes include pain interference and pain intensity as measured by instruments from the National Institute of Health's Patient-Reported Outcomes Measurement Information System (PROMIS) and psychological flexibility (chronic pain and cancer specific) as measured by The Chronic

Pain Acceptance Questionnaire and The Cancer Acceptance and Action Questionnaire.

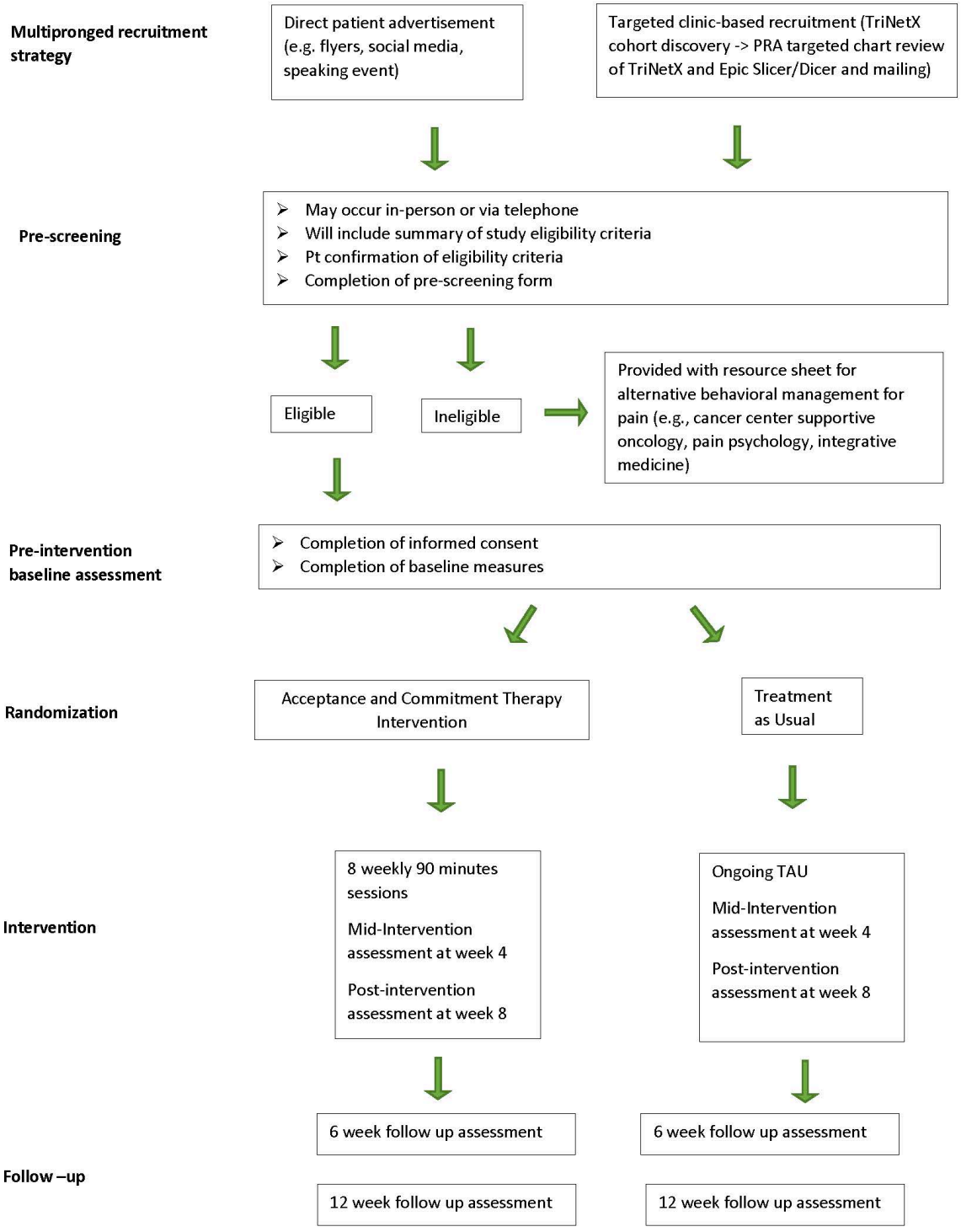
Population:

- ***Sample size:***
  - *Maximum number of participants that can be enrolled is 140*
  - *Minimum number of participants to be enrolled 50 (number of participants needed to answer feasibility aim)*
- ***Gender:*** *Male and Female*
- ***Age Range:*** *18-100*
- ***Demographic group:*** *Ambulatory outpatient oncology*
- ***General health status:*** *Chronic pain, ≥ three months since active treatment (e.g., chemotherapy, radiation, surgery)*
- ***Geographic location:*** *University of Colorado Cancer Center*

Number of Participating Sites enrolling participants: *1 (University of Colorado Cancer Center)*

Study Duration: *3 years*

SCHEMATIC OF STUDY DESIGN



1 PARTICIPATING SITES

A complete and current listing of investigators, research personnel, research facilities and other study centers (if applicable) participating in this study will be maintained throughout the duration of this study

2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 BACKGROUND INFORMATION

As the number of cancer survivors in the United States grows, so too does the occurrence of chronic, cancer-related pain conditions. Combinations of surgical treatment, radiation, and chemotherapy can contribute to various chronic pain syndromes in cancer survivors that can last long after active treatment has ended. It is estimated that nearly 40% of cancer survivors experience cancer-related pain (CRP) following completion of active treatment [1].

Five and ten year cancer survival rates have shown a consistent increase [2], shining a light on the long-term effects of cancer treatment, including chronic CRP. It has been recommended that treatment guidelines for chronic CRP mirror those already established for other chronic pain conditions, which often recommend a holistic approach facilitating pain relief as well as rehabilitation [3, 4]. Behavioral treatments are a key component to this approach, including psychological interventions, which have shown significant positive effects on pain severity and interference during treatment [5, 6]. Until recently, research for CRP has focused on procedure-related pain or pain during active treatment. There is relatively little intervention data on pain management following active treatment, creating a gap in the literature regarding strongly supported behavioral treatments for CRP in extended survivorship [6]. Applying efficacious pain management interventions from other chronic pain populations, assessing their effectiveness in chronic CRP, and evaluating their implementation are important next steps in this area of survivorship care.

Acceptance and Commitment Therapy is a theory-based treatment approach included under the broader Cognitive Behavioral Therapy umbrella. The core therapeutic process of ACT is psychological flexibility – the ability to continue in value-based behavioral engagement or change despite the presence of difficult sensations or cognitions. Acceptance and Commitment Therapy has been shown to be efficacious as an intervention for non-cancer chronic pain, specifically on outcomes of pain acceptance, psychological flexibility, functioning, anxiety, and depression [7, 8]. Acceptance and Commitment Therapy has also been shown to be feasibly delivered in cancer survivor populations for a variety of outcomes including quality of life [9, 10], disease related distress [11] and anxiety [12], and lifestyle change [13]. Though ACT has been used as an intervention for other types of pain management and with cancer populations, it has yet to be investigated as an effective and feasible treatment for survivors with chronic CRP. As the number of cancer survivors grows, addressing this chronic, disease-related issue will become a critical piece of providing high-quality cancer survivorship care.

2.2 RATIONALE

Until recently, research for CRP has focused on procedure-related pain or pain during active treatment. There is relatively little intervention data on pain management following active treatment, creating a gap in the literature regarding strongly supported behavioral treatments for CRP in extended survivorship. Applying efficacious pain management interventions from other chronic pain populations, assessing their feasibility and efficacy in chronic CRP are important next steps in this area of survivorship care.

Aim 1: To evaluate the implementation of an 8-week, group-based, Acceptance and Commitment Therapy (ACT) intervention for chronic pain management in cancer survivors who have completed active treatment.

Implementation outcomes will include acceptability, feasibility, and fidelity. Following completion of the intervention, semi-structured qualitative interviews with intervention group members will be used to assess participant acceptability of the ACT intervention content (e.g., complexity and credibility), as well as patients' feedback on intervention delivery. Additionally, weekly rating forms using Likert scales to collect quantitative data will be used to assess acceptability of content for each individual group therapy session. Feasibility will be evaluated through the collection of participant enrollment and adherence data throughout the intervention period and follow-up. Fidelity of the treatment will be measured through observation and the use of standardized checklist of core intervention components.

Aim 2: To evaluate the preliminary clinical efficacy of an 8-week, group-based, Acceptance and Commitment Therapy (ACT) intervention for chronic pain management in cancer survivors who have completed active treatment.

Participants (n = up to 140) will be randomly assigned to an ACT intervention and treatment as usual (TAU) or TAU alone. The ACT intervention will include eight weekly group sessions that will assist patients in developing skills to accept unhelpful internal events in order to clarify values and promote engagement in committed behaviors. The TAU condition will include medication management as directed by prescribing provider (e.g., physician), as well as access to Cancer Center supportive oncology services and other provider recommendations (e.g., acupuncture).

- **Changes in physical and emotional functioning** in the intervention group will be compared to the control group over time. The primary outcomes are physical and emotional functioning as measured by the SF-36. We hypothesize that improvements in physical and emotional functioning will occur in both groups over time but will be greater for the intervention group at completion of the program and at six and 12-week follow-ups as compared to the TAU group.

Aim 3: **To conduct exploratory analyses on pain interference, pain intensity, and psychological flexibility (chronic pain and cancer specific), which have been identified in the literature as secondary outcomes and process outcomes of ACT in chronic pain**.

- **Changes in pain interference, pain intensity, and psychological flexibility (chronic pain and cancer specific)** will be compared over time as exploratory outcomes between the intervention group and the TAU group. We hypothesize that improvement in these variables will occur in both groups over time but will be greater in the intervention group at completion of the program and at six and 12-week follow-ups.

2.3 POTENTIAL RISKS AND BENEFITS

2.3.1 KNOWN POTENTIAL RISKS

There are minimal risks to study participants. However, the ACT intervention, as well as measures included in assessment for all participants, will ask participants to reflect on both physical and psychological constructs that may be related to their cancer experience. This may result in distress. In the event that distress is acute, psychosocial support will be available for all participants. It is the expectation that participants in both groups will experience some benefit from active pain management intervention. All ACT groups will be directed by a licensed clinical psychologist in order to monitor for any distress in the group. Additionally, assessments of emotional functioning and pain experience (i.e., interference and severity) will be measured at the midpoint of the intervention in order to assess for any possible iatrogenic effect. These measures are precautionary in nature as there are no known potential risks for this intervention.

2.3.2 KNOWN POTENTIAL BENEFITS

The risks to participants are reasonable in relation to the anticipated benefits to participants and/or society, and in relation to the importance of the knowledge that may reasonably be expected to result, thereby falling in favor of performing the study:

- To Participant: This intervention has been found to improve functioning in non-cancer chronic pain populations. We hypothesize that it will also be effective with this sample.
- To Society: Effective and feasible behavioral interventions for chronic pain management are critical in order to meet the need for supportive care in our growing population of cancer survivors.
- Justify the importance of the knowledge gained: Improving our understanding of chronic pain management in cancer survivors and the feasibility of delivering the intervention will inform future research regarding symptom management in this population as well as direct clinical care in the field of psycho-oncology.

3 OBJECTIVES AND PURPOSE

- **Primary objective:** To evaluate the implementation of an 8-week, group-based ACT intervention for chronic pain management in cancer survivors who have completed active treatment.

- **Secondary objective:** To evaluate the preliminary clinical efficacy of an 8-week, group-based ACT intervention for chronic pain management in cancer survivors who have completed active treatment.

4 STUDY DESIGN AND ENDPOINTS

4.1 DESCRIPTION OF THE STUDY DESIGN

This study is a single site (University of Colorado Cancer Center), randomized control trial. It will investigate the implementation (i.e., feasibility, acceptability, and fidelity) and preliminary clinical efficacy of an ACT intervention plus TAU for chronic pain in cancer survivors compared to TAU alone. Following consent, participants will provide baseline data including demographic and clinical characteristics. Participants will be randomized to ACT plus TAU or TAU alone. Due to study design, it is not possible to blind either participants or investigators to study condition. Participants will complete assessments at baseline, 4-week intervention midpoint, 8-week intervention completion, 6-week follow-up, and 12-week follow-up.

4.2 STUDY ENDPOINTS

4.2.1 PRIMARY ENDPOINT

Implementation outcomes will include acceptability, feasibility, and fidelity. Following completion of the intervention, semi-structured qualitative interviews with intervention group members will be used to assess participant acceptability of the ACT intervention for management of chronic pain and value-based behavioral engagement. Additionally, weekly rating forms using Likert scales to collect quantitative data will be used to assess acceptability of content for each individual group therapy session. Feasibility will be evaluated through the collection of participant enrollment and adherence data throughout the intervention period and follow-up. Fidelity of the treatment will be measured through observation and the use of standardized checklist of core intervention components.

4.2.2 SECONDARY ENDPOINTS

Changes in physical and emotional functioning in the intervention group will be compared to the control group. The primary outcomes are physical and emotional functioning as measured by the

SF-36. We hypothesize that improvements in physical and emotional functioning will occur over time in both groups, but will be greater for the intervention group at completion of the program and at six and 12-week follow-ups as compared to the control group. The SF-36 has been used in previous studies evaluating ACT and chronic pain [14, 15]. Furthermore, the use of physical and emotional functioning as primary endpoints directly aligns with the theoretical basis of acceptance-based therapies [15]].

4.2.3 EXPLORATORY ENDPOINTS

Tertiary/exploratory outcomes include pain interference and pain intensity as measured by the National Institute of Health's PROMIS measures and psychological flexibility (chronic pain and cancer specific) as measured by The Chronic Pain Acceptance Questionnaire and the Cancer Acceptance and Action Questionnaire, respectively. These constructs have been previously supported as secondary outcomes and process outcomes of ACT in chronic pain populations [14, 15].

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 PARTICIPANT INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Provision to adhere to the consent form and verbally consent
2. Stated willingness to comply with all study procedures and be available for the duration of the study
3. Be a male or female aged 18-100
4. Have pathology confirmed diagnosis of a solid tumor cancer
5. Be three or more months out from active cancer treatment (surgery, chemotherapy, and/or radiation)
6. Endorses experiencing pain for three or more months prior to eligibility screening
7. Indicates moderate to severe difficulties with pain interference as related to their cancer experience, with a score of 4 or higher on the pain interference item from the Chronic Pain Grading Questionnaire
8. Shows no evidence of cancer disease (NED) or with stable, chronic disease under "watchful waiting"
9. Fluent in English
10. Psychiatric stability as assessed by chart review and study personnel (e.g., not exhibiting symptoms consistent with diagnoses of serious mental illness such as active psychosis or mania)
11. Ability to meet remotely via internet connection or over the phone.

5.2 PARTICIPANT EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Having pain that can be solely attributed to a diagnosis outside of their cancer experience
2. Presenting with barriers to group participation (e.g., social anxiety) or when group-based provision of care would impede participant's treatment or that of other group members
3. Patients with a diagnosis of malignant neoplasm of the brain (ICD-10 C71) or malignant neoplasm of spinal cord, cranial nerves and other parts of central nervous system (ICD-10 C72).

5.3 STRATEGIES FOR RECRUITMENT AND RETENTION

We will recruit participants from the University of Colorado Cancer Center. Recruitment will occur through a multipronged approach including direct advertisement to patients in the cancer center, as well as targeted recruitment based on cohort discovery through TriNetX and screening of the electronic health record (EHR)/EPIC, including use of the *Slicer Dicer* application.

Direct patient advertisement. Direct advertisement to patients will occur in the form of posted fliers and verbal advertisement at patient events (i.e., support groups). Participants will be provided with study information as well as research staff contact information, and they may contact research staff to express interest in participation. Staff will be available to discuss the study further with participants either in person or via telephone and will engage in eligibility screening if appropriate.

Electronic health record recruitment. Cohort discovery for feasibility will occur initially through TriNetX. Specifically, our initial cohort count will include patients with diagnoses of both a malignant neoplasm (see Table 1 for example codes) and relevant pain diagnoses (e.g., ICD-10 code G89.3- neoplasm related pain, ICD-10 code G62.0-chemotherapy induced neuropathy). In order to ensure a comprehensive list of relevant ICD-10 disease codes we will confer with clinical disease site co-investigators, CU Medicine billing, and/or EPIC resources. Following Institutional Review Board approval, this cohort will then be identified for further screening of eligibly criteria by research staff using both TriNetX and EPIC review in concert with the use of its application *Slicer Dicer*. Other institutional research databases approved by COMIRB may also be utilized for recruitment purposes. Disease site clinic leaders will be included as co-investigators for optimized clinical collaboration and recruitment. MRNs and PIDs will be used to create a key, and then screen participants in EPIC using this key. The study team will retain this key in a separate file from the main database until data collection is complete. Participants found to be eligible following EHR screening will initially be contacted via mail or email with information regarding the study. Mailings to patients will be sent on behalf of both the study PI and clinic director for the patient's relevant disease site. Participants will have the opportunity to "opt out" of further contact by study staff by contacting a provided telephone number.

Participants who do not choose to opt out will be contacted by research staff for further evaluation of interest in study participation and eligibility screening if appropriate.

Research staff will have a total of 3 independent points of contact with the patient, including the initial letter/email and two follow-up telephone calls. If possible, voicemail messages will be left at both follow-up telephone calls. This does not include points of contact from the research staff that are dependent on participant initiation of communication (i.e., calling a patient back after they have left a message). After receiving the letter/email and two telephone calls, the patient will no longer be contacted by research staff unless upon participant request.

If a participant has been screened during the "in person only" phase of this trial (1/1/2019 to April 1, 2020) and has indicated an interest in a virtual delivery of the intervention, they may be recontacted during the virtual phase (starting 4/28/2020).

Table 1. ICD-10 codes used for cohort discovery in TriNetX

Diagnosis	ICD-10 code
Malignant neoplasm of lip, oral cavity, and pharynx	C00-C14
Malignant neoplasms of digestive organs	C15-C26
Malignant neoplasm of respiratory and intrathoracic organs	C30-39
Malignant neoplasms of bone and articular cartilage	C40-C41
Melanoma and other malignant neoplasms of skin	C43-C44
Malignant neoplasm of mesothelial and soft tissue	C45-C49
Malignant neoplasm of breast (unqualified)	C50
Malignant neoplasm of female genital organs	C51-C58
Malignant neoplasms of male genital organs	C60-C63
Malignant neoplasms of urinary tract	C64-C68
Malignant neoplasms of thyroid and other endocrine glands	C73-C75
Malignant neoplasms of head, face, and neck	C76.0

The proposed sample size for recruitment is up to 140 with a minimum of 50. We expect attrition of 30% based on similar studies, as well as a conservative number of screening failures, yielding a resulting sample size of 50 participants for clinical outcome. We will use an RCT design, so that each group will consist of approximately 46 participants. With a maximum of 10 participants per ACT group, it is expected that between 4 to 10 0 intervention groups will be conducted to reach minimum/maximum enrollment goals. However, more groups can be conducted, depending on enrollment rates. These groups can run simultaneously, with the possibility of staggered start dates to accommodate accrual rates. In the event that accrual is slow and it takes several weeks to start ACT sessions, patients will always be able to withdraw from study participation and specific baseline measures (SF-36, PROMIS, CPAQ, and CAAQ) may need to be repeated if not within two weeks of intervention start.

5.4 PARTICIPANT WITHDRAWAL OR TERMINATION

5.4.1 REASONS FOR WITHDRAWAL OR TERMINATION

Participants are free to withdraw from participation in the study at any time upon request. An investigator may terminate participation in the study if any clinical adverse event (AE) or other medical or psychological condition or situation occurs such that continued participation in the study would not be in the best interest of the participant.

5.4.2 HANDLING OF PARTICIPANT WITHDRAWALS OR TERMINATION

Participants will be informed in the consent process that they may discontinue the study at any time.

5.5 PREMATURE TERMINATION OR SUSPENSION OF STUDY (STUDY STOPPING RULES)

As stated above, the anticipated risks of participating in this study are low. Should study PI (Studts) believe at any point in the study that participation is detrimental to the participant's health, they will end the subject's participation and refer the subject to other relevant treatment resources as appropriate (i.e., mental health resources).

If, after three consecutive months of active recruitment and enrollment, investigators are unable to sufficiently recruit patients to conduct a single intervention group, consideration of an alternative design (i.e., multiple baseline single arm) will be considered. Following modification of design due to low enrollment, if after three consecutive months of active recruitment and enrollment investigators are unable to sufficiently recruit patients to conduct a single intervention group, the trial will be considered not feasible for implementation and terminated.

6 STUDY THERAPY

6.1 STUDY THERAPY AND CONTROL DESCRIPTION

Intervention Groups

Treatment as usual. Treatment as usual will include ongoing provision of usual treatment options for pain management. This includes continued medication management for cancer related chronic pain by prescribing providers (e.g., oncologist, primary care provider), and access to supportive oncology services (e.g., social work). It may also include other behavioral pain management such as physical therapy, acupuncture, or massage. Psychotherapy (e.g., Cognitive Behavioral Therapy) is often used as TAU in chronic pain. All participants may pursue this treatment modality, as it is part of standard care; however, for participants randomized to the intervention condition, their specified psychotherapy will be the ACT group protocol. Data regarding participation in these services will be collected as stated above in section 5.3.

ACT Intervention. Intervention group participants will attend eight weekly, 90-minute, in person, group-based ACT sessions. Groups may occur in person or remotely (i.e., audio/visual teleconferencing). Groups will be initiated with no more than 10 participants and no fewer than 4 participants. If a new group is scheduled with 4-10 participants and enough patients are "no-shows" that cause the group number to fall below 4, the group will continue as is and this will not be considered a deviation. Sessions will be adapted from an efficacious ACT chronic pain treatment manual [14, 15]. Sessions will include key theoretical ACT constructs and strategies as they relate to chronic pain. A licensed clinical psychologist or licensed clinical social worker trained in ACT will facilitate all sessions. Participants in the ACT intervention group will also continue to receive medication management and other behavioral management interventions as described above in "treatment as usual". Data regarding participation in these services will be collected as stated below in section 7.1.

See Table 2 for more detail.

Table 2. ACT Intervention Constructs/Targets

ACT Session	Topic/Targeted Component	Aims/Application to Chronic Pain
Session 1 – Introductions and Basic Foundations of Treatment	• Group Introductions • Introduction to Chronic Pain and Cancer • Creative Hopelessness	• Group introductions and ground rules • Familiarizing group members with the treatment aims • Evaluate the usefulness of previous control strategies for pain • Foster psychological flexibility and awareness around the difficulty of controlling pain
Session 2 – Options and Setting a Course for Treatment	• Behavior Change • Mindfulness	• Introduction, discussion and application of the tripartite behavioral model in order to understand how thoughts and emotions impact behaviors • Introduction to mindfulness practice
Session 3 – "Learning to Live" with Chronic Pain	• Acceptance • Values • Mindfulness	• Foster acceptance around unhelpful internal events that may get in the way of coping around chronic pain • Identifying and clarifying personal values • Continued development of mindfulness practice
Session 4 – Values and Action	• Values • Goal Setting • Committed Action • Mindfulness	• Continued clarification of personal values • Differentiating values and goals • Understanding barriers that might occur when engaging in valued actions • Continued mindfulness practice
Session 5 – Urges, Thoughts, & Feelings	• Cognitive Defusion • Mindfulness	• Introduction to concept of cognitive defusion • Practice creating space between unhelpful thoughts that may increase suffering or interfere with valued behaviors • Continued mindfulness practice

Session 6 – Action-Getting Your Feet Moving	• Treatment Review • Committed Action • Mindfulness	• Review of treatment progress and any areas of ongoing concern • Planning for action • Fostering willingness around potential internal barriers • Continued mindfulness practice
Session 7 – Commitment	• Willingness • Committed Action • Mindfulness	• Extended discussion of willingness • Fostering commitment to actions and values even in the face of barriers • Continued mindfulness practice
Session 8 – Lifelong Maintenance	• Maintenance	• Fostering commitment • Relapse prevention and setbacks • Saying goodbye to group

6.1.1 DURATION OF THERAPY

For the ACT intervention group, an 8-week therapy protocol will be used.

6.1.2 TRACKING OF THERAPY

Attendance to weekly group sessions will be tracked in order to monitor the number of therapy sessions received.

7 STUDY PROCEDURES AND SCHEDULE

7.1 STUDY PROCEDURES/EVALUATIONS

After a participant has been consented, he or she will be randomized to either the ACT intervention group or the TAU condition as described in section 6.1. All participants will complete baseline, mid-point, post-intervention, and follow-up assessments. Further information for each assessment time point is provided below in this document under section 7.2. Also, see Table 3 for assessment schedule.

Table 3. Assessment schedule for all study participants

Assessments/ Measures	Baseline Assessment	Intervention Mid-Point (Wk 4) and Post-Intervention (Wk 8)	6 Wk Follow-up	12 Wk Follow-Up
Physical/Emotional Functioning (SF-36)	X	X	X	X
Pain Interference/Intensity (PROMIS)	X	X	X	X
Psychological Flexibility measures (CPAQ and CAAQ)	X	X	X	X

Study measures will include the following:

Adherence. Adherence to the intervention will be measured by completion of all relevant assessments and, for intervention group members, attendance to therapy sessions as outlined above and completion relevant assessments.

Fidelity. Fidelity of intervention delivery will be evaluated through structured observational methods. Third-party observers (i.e., not provider or participant) will complete a checklist instrument including all components of the active intervention.

Demographic information. Relevant demographic information (e.g., sex, ethnicity, race, education level, marital status, etc.) will be collected from the patient at the pre-intervention assessments (screening and/or baseline), and when necessary, confirmed via EHR. In the case that the electronic chart and patient report differ, patient report will be given priority.

Medical information. Relevant medical information will be collected both from the patient at the pre-intervention assessments as well as from chart review of the University of Colorado Hospital electronic health record (EHR). When patient report and EHR are in conflict, EHR data will be preferred. Relevant medical information includes medications pertaining to pain management (e.g., opioid and non-opioid analgesics), medical pain management services (e.g., nerve blocks, spinal cord stimulator), behavioral pain management services (e.g., massage, acupuncture, physical therapy), and medications pertaining to psychiatric symptoms (given their impact on the primary outcome). Other relevant medical information will include data directly related to the patient's cancer treatment, including diagnosis, as well as type and duration of treatment.

Physical/Emotional Functioning. The Medical Outcomes Study 36-item short-form health survey (SF-36) is a self-report measure of health related quality of life that includes subscales for both physical functioning and emotional well-being [17]. The physical functioning subscale includes 10 items evaluating the occurrence and severity of physical difficulties, with a higher subscale score indicating better levels of physical functioning. The subscale specifically asks, "Does your health now limit you in these activities? If so, how much?", and then provides a number of activities related to daily living (e.g., climbing stairs, bathing or dressing) as well as exercise behaviors (e.g., walking more than one mile, vigorous activities such as strenuous sports). Item responses are made on a 3-point Likert scale with one indicating "Yes, limited a lot," two indicating "Yes, limited a little," and three indicating "No, not limited at all." This subscale has excellent internal consistency with a Cronbach's alpha of .93 [18].

The emotional well-being subscale of the SF-36 includes five items evaluating how patients have felt during a previously identified period, with a higher subscale score indicating higher levels of positive affect. Specifically, items ask questions such as "Have you been a very nervous person?" and "Have you felt calm and peaceful?" Item responses are made on a six point Likert scale with one indicating "All of the time" and six indicating "none of the time." This subscale has excellent internal consistency with a Cronbach's alpha of .90 [18].

Pain Intensity and Interference. The National Institute of Health's Patient-Reported Outcomes Measurement Information System (PROMIS) pain intensity instrument evaluates how much a person hurts [20]. This study will use the PROMIS Scale v1.0- Pain Intensity 3a short form, which assesses pain intensity over seven days using two items, including pain intensity at its worst and average pain intensity. It also evaluates current pain levels. All items are rated on a 1-5 rating scale with 1 as "had no pain" and 5 as "very severe". The pain interference instrument [21] evaluates the impact of pain on various domains of living, including participation in social, cognitive, emotional, physical, and recreational activities. This study will use the PROMIS scale v1.0- Pain Interference 8a, which includes eight total items asking the patient to recall the extent of pain interference over the past seven days. All items are rated on a 1-5 rating scale with 1 as "not at all" and 5 as "very much". For all items in the PROMIS pain item bank the score metric is Item Response Theory (IRT). Both measures provide an IRT-based T-score and Standard Error [20, 21].

Psychological Flexibility Measures. The Chronic Pain Acceptance Questionnaire (CPAQ [19]) is a 20-item self-report measure of experiential acceptance in pain populations. This measure has two unique and psychometrically reliable subscales, including activity engagement ($\alpha = .82$) and pain willingness ($\alpha = .78$) [19]. Examples of items from the activities engagement subscale include "There are activities I do when I feel pain" and "I lead a full life even though I have chronic pain." Examples of items from the pain willingness subscale include "I need to concentrate on getting rid of my pain" and "I avoid putting myself in situations where my pain might increase." A 0-6 Likert rating scale indicates how true each statement is for the patient with 0 as "never true" and 6 as "always true."

The Cancer Acceptance and Action Questionnaire (CAAQ [20]) is an 18-item self-report measure of disease specific experiential avoidance. Items on this measure have been adapted from other disease specific versions of the Acceptance and Action Questionnaire [21] to the cancer experience. For example, items include statements such as "I try to avoid reminders of my cancer" and then participants are asked to rate how true this statement is on a 1-7 Likert scale

with one as "never true" and 7 as "always true." This measure has shown excellent internal consistency when used in a heterogeneous cancer sample (α = .91-.95) [20].

7.2 STUDY SCHEDULE

7.2.1 SCREENING

Participant Screening and Assessment

Participant screening. In addition to screening conducted via recruitment methods described above, all participants will be screened either in person,via telephone, or video conference with a standardized screening form. Verbal consent will be obtained by research staff prior to administering the standardized screening form, which will be included on the screening form. The screening form will assess 1) inclusion criteria, 2) exclusion criteria and 3) a pain interference measure. The pain interference measure will include a single item pulled from the Chronic Pain Grading Questionnaire [23]. Participants eligible for the study will rate their level of interference with their daily activities from their cancer-related pain as 4 or higher on a scale of 0 = no interference to 10 = unable to carry on any activities. This scale has been used as a screening tool in similar psychotherapy trials for non-cancer related chronic pain [18]. After verbally consenting, eligible participants will be randomized to either the ACT plus TAU intervention condition or the TAU alone condition. Participants found to be ineligible will be provided with a packet for alternative resources for interdisciplinary pain management (e.g., CU pain psychology services and CU integrative medicine services) either in person or via email.

7.2.2 ENROLLMENT/BASELINE

Baseline Assessment. Eligible participants will be scheduled for an initial baseline appointment with research staff held either in person or done remotely (i.e., video conference or over the phone). During this baseline appointment, participants will complete the informed consent process and all questions will be answered by research staff. After providing consent, participants will be randomized. Patients will then be asked to complete their baseline measures, if it is feasible; however, participants may also have the option of completing these measures via a REDCap HIPAA secure link from their own personal computer. Baseline assessment measures will be completed within a two-week period prior to the initiation of the intervention. For patients who are randomized to the TAU arm, the next time point after baseline will be the Week 4 assessments, which should be completed at 4 weeks (+/- 7 days) of the baseline assessments. For patients who are randomized to the ACT arm, the next time point after baseline will be the scheduled Week 1 ACT intervention group session. Specific baseline measures (SF-36, PROMIS, CPAQ, and CAAQ) may be repeated in order to be within the specified two-week window.

7.2.3 INTERVENTION AND FOLLOW-UP

Intervention and Follow-up Assessments. All study participants will complete study related assessments/measures at mid-intervention (week 4, +/- 7 days), post-intervention (week 8, +/- 7 days), and at the 6-week (+/- 7 days) and 12-week (+/- 7 days) follow-ups. It is expected that all assessments will be delivered via REDCap Survey. For in person patients, a tablet will be available for participants to use at the UCCC if they are not able to access internet otherwise. For all virtual participants, surveys must be completed via the REDCap link. If participants do not have a valid email address then surveys may be completed by paper and pencil or over the phone with research staff. REDCap is a secure web application designed to support data capture for research studies, provider user-friendly web-based case report forms, real-time data entry validation, audit trails and a de-identified data export mechanism to common statistical packages. Participants will be compensated with $10.00 gift cards for completing six and 12-week follow-up assessments. See section 7.2.7 for full quantitative assessment schedule.

7.2.4 FINAL STUDY VISIT

Qualitative interview appointment. Participants randomized to the intervention group may also be asked to participate in qualitative interviews regarding the acceptability of the intervention content and delivery following all quantitative assessment follow-up visits (any time during Week 9 through the 12-Week follow-up). Their invitation for participation will be determined by saturation of the data as explicated in the analysis portion of this document. Specifically, these data will be gathered through one-on-one, standardized open-ended interviews [22]. Interviews will be conducted using a semi-structured interview protocol [23], given either in person or over the telephone. The interview will be recorded, so that it can be transcribed and analyzed appropriately. Interviews will last approximately 30-45 minutes. Participants will be compensated with $15.00 gift cards for completing this interview.

7.2.5 EARLY TERMINATION VISIT

If the participant chooses to terminate participation early, he or she will be contacted either in person or by phone to verify the decision to discontinue the study.

7.2.6 UNSCHEDULED VISIT

ACT intervention participants who are unable to attend a group session will be offered an individual session in order to review material with the group provider. This includes “make-up” sessions, which may occur due to planned or unplanned events (e.g., vacation or illness). “Make-up” sessions must occur (any time) prior to next scheduled session. These sessions will be scheduled based on the availability of both the participant and the provider. The make-up session may occur either in-person or remotely.

7.2.7 SCHEDULE OF EVENTS TABLE

	Screening	Baseline	8-week intervention period[7]								Follow-up Assessments[7]		Qualitative Interview
			Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Post 6-Wk[5]	Post 12-Wk[5]	
Consent		X											
Pre-Screen	X												
Eligibility		X											
Demographics	X	X											
Randomization[2]		X											
ACT session 1[3]			X										
ACT session 2[3]				X									
ACT session 3[3]					X								
ACT session 4[3]						X							
ACT session 5[3]							X						
ACT session 6[3]								X					
ACT session 7[3]									X				
ACT session 8[3]										X			
Likert Scale – Acceptibility[3]			X	X	X	X	X	X	X	X			
SF-36		X[4]				X[5]				X[5]	X[5]	X[5]	
PROMIS		X[4]				X[5]				X[5]	X[5]	X[5]	
CPAQ		X[4]				X[5]				X[5]	X[5]	X[5]	
CAAQ		X[4]				X[5]				X[5]	X[5]	X[5]	
Qualitative Interview[3,6]													X

1. Determined by pre-screen chart review, screening phone call (with verbal consent), and confirmation of eligibility by research study personnel, after patient consents.
2. After consent and before completion of baseline measures.
3. ACT (intervention) participants only.
4. Within 2 weeks prior to intervention start date. These measures may be repeated in order to be within window.
5. +/- 7 day window
6. The qualitative interview may be conducted via phone or in person, any time from Week 9 through 12-Week follow-up; for ACT participants only.

7. Intervention and Follow up visits can be completed in person or remotely.

7.3 CONCOMITANT MEDICATIONS, TREATMENTS, AND PROCEDURES

All concomitant pain and psychiatric prescription medications taken during study participation will be recorded on the case report forms (CRFs). For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications reported in the CRF include concomitant pain and psychiatric prescription medications, over-the-counter pain medications, and non-prescription pain medications.
In addition, information will be gathered about other treatments for pain, including acupuncture, massage, and physical therapy for each patient.

7.4 PROHIBITED TREATMENTS AND PROCEDURES

Treatment with other psychotherapies focused on pain management (i.e., cognitive behavioral therapy) will not be permitted for ACT intervention group members.

8 ASSESSMENT OF SAFETY

8.1 SPECIFICATION OF SAFETY PARAMETERS

All participants consenting to study participation will be provided with the contact information for the PI, Dr. Jamie L. Studts, who is a licensed clinical psychologists and a provider at the Cancer Center. All participants will have access to psychosocial support services available at the Cancer Center.

8.1.1 DEFINITION OF ADVERSE EVENTS (AE)

The following are considered to be adverse events:

- Increase in symptoms of depression and/or anxiety directly related to the act of participating in the intervention (i.e., scheduling appointments, additional visits).
- Increase in symptoms of depression and/or anxiety directly related to material presented in the intervention or the focus groups.
- Increases in anxiety and/or depression related to cancer diagnosis, treatment, impact of treatment on functioning and treatment side effects are **not** considered adverse events.

8.1.2 DEFINITION OF UNANTICIPATED PROBLEMS (UAP)

This study will use the COMIRB definition of UAP.

- Any event or information that was unforeseen and indicates that the research procedures caused harm (including physical, psychological, economic, or social harm) to participants or others or indicates that participants or others are at increased risk of harm than was previously known or recognized.

8.2 CLASSIFICATION OF AN ADVERSE EVENT

8.2.1 SEVERITY OF EVENT

For AEs not included in the protocol-defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life threatening or incapacitating.

8.2.2 EXPECTED ADVERSE EVENTS

The PI, Jamie L. Studts, PhD will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.3 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until the completion of the 12-Week follow-up measures. At each study visit, the investigator will inquire about the occurrence of AE/ SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.4 REPORTING PROCEDURES

8.4.1 ADVERSE EVENT REPORTING

The sponsor-investigator must record non-serious adverse events and report to DSMC and IRB according to timetable for reporting specified in the Data Safety Monitoring Plan and per COMIRB's reporting requirements. Reporting will be done by the OCRST and Dr. Studts.

8.4.2 UNANTICIPATED PROBLEM REPORTING

This study will follow COMIRB's guidance for UAP reporting and the DSMC's requirements (discussed below). AEs, noncompliance and protocol violations will be recorded and reported as required either promptly (within 5 days of Sponsor-Investigator's knowledge) or at the time of the study's continuing review.

It is the responsibility of the OCRST and PI to report incidents or events that meet the criteria for UAPs reporting to their IRB using the IRB's standard UAP form. The OCRST and PI are responsible for reporting the UAP to the UCCC DSMC, if applicable.

8.5 SAFETY OVERSIGHT

The principal investigator will be responsible for the conduct of this study, overseeing participant safety, executing the data and safety monitoring (DSM) plan, and complying with all reporting requirements to local and federal authorities. This oversight will be accomplished through additional oversight from the Data and Safety Monitoring Committee (DSMC) at the University of Colorado Cancer Center (CU Cancer Center). The DSMC is responsible for ensuring data quality and study participant safety for all trials at the CU Cancer Center. A summary of the DSMC's relevant activities is as follows:

- Conduct of internal audits
- May submit recommendations for corrective actions to the CU Cancer Center's Executive Committee

Study audits conducted by the DSMC will consist of a review of the regulatory documents, consent forms, and source data verification. Documentation of the audit conducted by the DSMC will then need to be submitted to the IRB of record at the time of the IRB's continuing review of this trial (if applicable).

9 CLINICAL MONITORING

Clinical site monitoring will be conducted to ensure that the rights and well-being of human participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/ amendment(s), with GCP, and with applicable regulatory requirement(s).

Monitoring for this study will be performed by CU Cancer Center Clinical Monitor in accordance with the clinical monitoring plan (CMP), incorporated herein by reference. The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of the monitoring reports.

Independent audits will be conducted by the CU Cancer Center DSMC to ensure monitoring practices are performed consistently across all participating sites, if applicable, and that monitors are following the CMP.

10 STATISTICAL CONSIDERATIONS

10.1 STATISTICAL HYPOTHESES

- Primary Efficacy Endpoint(s):
  Participants will find the intervention acceptable. Implementation of intervention will be feasible.

- Secondary Efficacy Endpoint(s):

10.2 ANALYSIS DATASETS

An intention-to-treat analysis dataset will be used for this study. The dataset will include demographic and clinical information from each participant's medical chart, as well as self-report data provided by each participant.

10.3 DESCRIPTION OF STATISTICAL METHODS

10.3.1 GENERAL APPROACH

This study will employ an effectiveness-implementation hybrid design (Type 1) [14], including a randomized controlled trial.

- Descriptive statistics: Categorical data will be presented as frequencies and percentages. Continuous variables will be presented using appropriate measures of central tendency.
- Inferential tests: Inferential tests will be one-tailed using an alpha level of .05.
- Covariates: We will compare treatment and control groups across all relevant demographic and medical variables to ensure randomization resulted in an equal distribution across groups. If differences are found among these variables, they will be included as covariates and subsequent models.
- For all dependent variables, we will check for normality by examining skew and kurtosis. For variables that violate normality, we will use nonparametric bootstrapping to estimate standard error and 95% confidence intervals. Additionally, we will also assess the data for violations of sphericity.

10.3.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

The purpose of the qualitative data analysis, which will address the primary aim of this project, is an in-depth understanding of patients' perceived usefulness of the ACT intervention for promoting management of chronic pain. Analysis will begin with the transcription of each semi-structured interview into the coding software program. Qualitative analyses will be conducted using ATLAS.ti software, which will store, code, and categorize data transcripts. For this project data will be analyzed with a constant comparative approach [24]. This is an inductive approach to data analysis through which each piece of data (e.g., statement, emerging theme, etc.) is compared to other pieces of data and evaluated for similarities and/or differences.

Quantitative data regarding acceptability will also be collected from intervention participants through the use of weekly rating forms using Likert scales. These will be used to assess individual intervention sessions/topics. Descriptive statistics including frequencies and measures of central tendency will be calculated from these data. These acceptability scales may be administered in person or digitally.

10.3.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Repeated measures ANOVA will be used to test the effect of the treatment on the outcomes over time. In regards to the hypotheses related to specific aim 1, outcomes including physical/emotional functioning, will be compared between treatment groups using separate repeated measures ANOVA with 5 measurement time points. Data will be presented as unstandardized beta coefficients and their respective standard errors. T-tests and chi-squares will be used to compare demographic variables between participants who complete the study and those who do not. Listwise deletion will be used when data is not missing for more the 10% of participants and there are no differences on demographic variables between completers and non-completers. If data are missing for more than 10% of participants or if there are demographic

differences between completers and non-completers, Full Information Maximum Likelihood will be used to estimate missing data.

10.3.4 ADHERENCE AND RETENTION ANALYSES

Feasibility is a key outcome of the implementation aim for this study. Participant eligibility, enrollment, and completion of study intervention and assessments will be tracked through standardized databases (e.g., screening and enrollment). We will also track completion of assessment measures through REDCap. Percentages for each relevant domain will be calculated. Individuals who do not complete assessment time points as prescribed will be contacted by research staff in order to minimize missing data. Participants who choose to withdraw from the study will be contacted to confirm their decision and will be asked why they are choosing to discontinue participations (e.g., time, medical issues, does not feel intervention is helpful). This information will be used to inform future studies and relevant grant applications.

10.3.5 BASELINE DESCRIPTIVE STATISTICS

Relevant demographic constructs (i.e., age, race/ethnicity), as well as baseline assessments of primary and exploratory measures (e.g., physical and emotional functioning, pain severity and intensity, and measures of psychological flexibility), will be compared using two sample t-tests and chi-square analyses.

10.3.6 PLANNED INTERIM ANALYSES

Given that the secondary aim is feasibility and the exploratory aim is to test possible process measures, study investigators will monitor data throughout the project.

10.3.7 ADDITIONAL SUB-GROUP ANALYSES

Subgroup analyses comparing outcomes for participants who received the intervention in-person versus those who received the intervention remotely will be conducted.

10.3.8 MULTIPLE COMPARISON/MULTIPLICITY

Multiple comparisons are not an area of concern for our study design.

10.3.9 TABULATION OF INDIVIDUAL RESPONSE DATA

Individual data will be entered into REDCap using each patient's unique study identification number and will be listed by measure and time point.

10.3.10 EXPLORATORY ANALYSES

Repeated measures ANOVA will be used to test the effect of the treatment on the outcomes over time. Exploratory outcomes pain interference, pain intensity, and psychological flexibility, will be compared between treatment groups using separate repeated measures ANOVA with five measurement time points. Data will be presented as unstandardized beta coefficients and their respective standard errors. T-tests and chi-squares will be used to compare demographic variables between participants who complete the study and those who do not. Listwise deletion will be used when data is not missing for more than 10% of participants and there are no differences on demographic variables between completers and non-completers. If data are missing for more than 10% of participants or if there are demographic differences between completers and non-completers, Full Information Maximum Likelihood will be used to estimate missing data. Exploratory mediation analyses of exploratory process measures will also be conducted.

10.4 SAMPLE SIZE

Aim 1:

Given that the primary aim of this study is the feasibility of implementation, a minimum of n = 50 will be set for recruitment. This is generally discussed as a moderate sample size in feasibility pilot studies in clinical research [25-27].

In qualitative research, it is generally accepted that data collection continues until "saturation" has been met [28]. Saturation occurs once a researcher has collected enough case data that data provided by additional cases does not provide new information or themes. It has been suggested, for studies that utilize individualized interviews to develop and understand nuances of theory, that between 12-30 participants are typically needed to reach saturation [28, 29]. This will be the targeted sample size range for the qualitative interviews.

Aim 2:

A previous study of ACT for chronic pain management [30], using the same measures of physical and emotional functioning (e.g., the SF-36), found moderate (d = 0.61) to large effects (d = 0.97) at post treatment, respectively. Sample size was estimated using d = 0.61, with power at 0.80 and α = .05, two-tailed. It is assumed that the correlation between pre and post-test measures will be high at .5. With these parameters and using repeated measures ANOVA to evaluate treatment difference, sample size is powered for clinical outcomes at 92 participants; with an estimated 30% attrition and conservatively including the possibility of screening failures, a maximum sample of 140 participants will be targeted for enrollment. Power was calculated using the FactorialPowerPlan Macro for SAS. See above section 10.3.2 for

missing data plan. The maximum number of participants that can be enrolled is 140, allowing for 30 % attrition and possible screening failures.

10.5 MEASURES TO MINIMIZE BIAS

10.5.1 ENROLLMENT/ RANDOMIZATION/ MASKING PROCEDURES

There is no blinding in this study. Enrolled participants will be randomly assigned at a 1:1 ratio to receive eight weekly group-based ACT sessions plus TAU or TAU alone. The REDCap randomization tool will be used to facilitate randomization.

11 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Appropriate research records will be maintained as necessary and in compliance with regulatory and institutional requirements for the protection of confidentiality of participants.

It is expected that the majority of data collection will occur via REDCap, so it is likely any creation of source documents will be minimal.

This study may collect source data from hospital records, fidelity checklists, paper versions of questionnaires, recorded audio tapes and transcriptions of interviews. These will be kept in de-identified labeled binders/folders in a locked cabinet in a locked office.

12 QUALITY ASSURANCE AND QUALITY CONTROL

Quality Control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/ resolution.

Following written SOPs, the study monitor will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial-related sites, source data/ documents, and reports for the purpose of monitoring and auditing by the DSMC audit team, and inspection by local and regulatory authorities.

13 ETHICS/PROTECTION OF HUMAN SUBJECTS

13.1 ETHICAL STANDARD

The PI will ensure that this study is conducted in full conformity with regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56. ICH E6 may also be followed to the extent it has been adopted by and is in accordance with FDA regulations.

13.2 INSTITUTIONAL REVIEW BOARD

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the Colorado Multiple Institutional Review Board (COMIRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by COMIRB before the changes are implemented to the study. All changes to the consent form will COMIRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

13.3 INFORMED CONSENT PROCESS

13.3.1 CONSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study procedures and risks are given to the participant. Consent may occur in person or remotely (i.e., video and/or telephone).

13.3.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent process will be initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families.

Consent forms will be IRB-approved and the participant will receive a copy of the consent document either via mail or email to read and review prior to the consent process. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants.

Participants will have the opportunity to carefully review the consent form and ask questions prior to verbally consenting to participate. The participants will have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will verbally consent either over the phone or via videoconference prior to any procedures being done specifically for the study.

The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

13.4 PARTICIPANT AND DATA CONFIDENTIALITY

Participant confidentiality is strictly held in trust by the participating PIs, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, or representatives of the IRB may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the University of Colorado Cancer Center. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by the University of Colorado Cancer Center research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the University of Colorado Cancer Center.

14 DATA HANDLING AND RECORD KEEPING

14.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the research study assistant under the supervision of the site PI. The PI is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. Study data will be collected and managed using REDCap (Research Electronic Data Capture), a HIPAA-compliant research data management system.

14.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 7 years after formal discontinuation of in conformance with the applicable regulatory requirement(s). These documents should be retained for a longer period, however, if required by local regulations, or institution policies. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the PI when these documents no longer need to be retained.

14.3 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or SOP requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly. These practices are consistent with ICH E6, sections:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3.
- 5.1 Quality Assurance and Quality Control, section 5.1.1.
- 5.20 Noncompliance, sections 5.20.1 and 5.20.2.

It is the responsibility of the study team to use continuous vigilance to identify and report deviations. All deviations must be addressed in study source documents, reported to COMIRB. Protocol deviations must be sent to the local IRB per their guidelines. The site PI/ study staff is responsible for knowing and adhering to their IRB requirements. Further details about the handling of protocol deviations will be included in the SOP and/or study procedures manual.

15 STUDY ADMINISTRATION

15.1 STUDY LEADERSHIP

Study leadership will include the principal investigator, Jamie L. Studts, PhD.

16 CONFLICT OF INTEREST POLICY

Independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed by the University of Colorado Denver's (UCD) Office of Regulatory Compliance Conflict of Interest and Commitment Management (COIC) program. Persons with a perceived conflict of interest will have such conflicts managed in a way that is appropriate to their participation in the trial. Conflict of Interest management plans are project-specific and are reviewed at least annually. UCD has integrated the institutional conflict of interest management program with its existing program.

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Study Title: **Acceptance and Commitment Therapy for Chronic Pain in Cancer Survivors**

Principal Investigator: **Emily Cox-Martin, PhD**

COMIRB No: **18-1102**

Version Date: **July 15, 2020**

Thank you for your interest in this study on chronic pain in cancer survivors.

The purpose of this study is to see if an 8-week, group-based, Acceptance and Commitment Therapy (ACT) intervention for chronic pain management in cancer survivors who have completed active treatment is feasible. ACT is a behavioral therapy that includes mindfulness practice and has been shown to be helpful in managing other types of non-malignant chronic pain. You are being asked to be in this research study because you have been identified as a patient who has completed active cancer treatment who may also be having difficulty with chronic pain.

If you join the study, you will be asked to adhere to the consent form and verbally consent Once you have verbally agreed to participate, you will be "randomized" into one of two study groups. The first group will receive treatment as usual, which includes ongoing care as directed by your oncologist or primary medical provider, and may/may not include medication management, interventional pain management, or behavioral pain management, and access to supportive care services in the cancer center. The second group will also receive the treatment as usual described above, with the exception that they cannot receive psychotherapy for chronic pain management outside of the psychotherapy provided through participation in the study. In addition, the second group will also receive an Acceptance and Commitment Therapy (ACT) intervention. This intervention includes weekly group sessions that aim in assisting patients in developing skills to cope with unhelpful feelings or sensations related to chronic pain and move forward with important goals. . You have an equal chance of being placed in each group, and neither you nor the study team can chose the group you are placed in.

<u>Study Procedures:</u>

Before you start the study we will record demographic information (e.g. your date of birth, race, ethnicity), and complete medical history. This history will look at the background and progress of your cancer and any treatments you have received for your disease, as well as your treatment for pain

management.

Regardless of group, you will be asked to complete questionnaires at 5 time points throughout the course of this study, which will ask about pain intensity/interference and physical/emotional functioning.

ACT intervention therapy group consists of eight weekly, 90-minute, group-based sessions. If you are unable to attend a session, we will try to schedule a make-up session for you. A licensed clinical psychologist or licensed clinical social worker trained in ACT will facilitate all sessions. Sessions will be adapted from an 8-week therapy protocol and will include strategies as they relate to handling chronic pain. After each session, you will be asked to rate the value of that day's session.

The as Usual group involves access to psychosocial support available through UC Cancer Center and ongoing care as directed by your primary provider as mentioned previously.

As mentioned above, patients randomized to the ACT (intervention) group will be asked to rate the helpfulness of each of the eight weekly therapy sessions. Participants may also be asked to complete a follow-up intervention following the 8 week intervention. It can be completed over the phone and will include speaking with study staff about the ACT intervention. These interviews will be recorded (for research purposes only and not for treatment), so that they can be transcribed and analyzed appropriately.

Possible discomfort or risks include experiencing emotional and/or psychological discomfort when asked questions about emotional and physical functioning, and basic demographics. Please feel free to skip any questions that make you feel uncomfortable. The other possible risk is the loss of confidentiality. We will do all that we can to protect your information, but it cannot be guaranteed.
There may also be risks the researchers have not thought of.

Every effort will be made to protect your privacy and confidentiality by ensuring that no names or medical record numbers will be used on the questionnaire or in any study database used for analyses. Study staff will assign a research identification number to each participant that will be used on the questionnaire. Only Dr. Cox-Martin and the study staff will have access to the key linking research identification numbers to participants' names. This key will be kept in a secure electronic file that is password protected.

This research is being paid for by The National Cancer Institute and The University of Colorado Cancer Center

This study is not designed to benefit you directly. You have a choice about being in this study. You do not have to be in this study if you do not want to be.

This study has been issued a Certificate of Confidentiality from the federal government to help protect your privacy. The Certificate prohibits the researchers from disclosing your name, or any identifiable information, document or biospecimen from the research, with the exceptions listed below. A certificate provides protections against disclosing research information in federal, state, or local civil, criminal, administrative, legislative or other proceedings.

These protections apply only to your research records. The protections do not apply to your medical records.

The data we collect will be used for this study, but may also be important for future research. Your data may be used for future research or distributed to other researchers for future study without additional consent if information that identifies you is removed from the data.

If you have questions, you can email Emily Cox-Martin, PhD at Emily.Cox-Martin@cuanschutz.edu . You can email to ask questions at any time.

You may have questions about your rights as someone in this study. If you have questions, you can call COMIRB (the responsible Institutional Review Board) at (303) 724-1055