Effect of guided imagery for radiotherapy-related distress: A randomized controlled trial for patients with head and neck cancer.

Protocol Number:	18-1100
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Funded by:	University of Colorado American Cancer Society Institutional Research Grants University of Colorado Cancer Center Investigator Initiated Trials Program (regulatory support)
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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
GI	Guided imagery
HNC	Head and neck cancer
IIT	Investigator-Initiated Trial
RT	Radiotherapy
TLFB	Time line follow-back

PROTOCOL SUMMARY / SYNOPSIS

Protocol Title:

Effect of guided imagery for radiotherapy-related distress: A randomized controlled trial for patients with head and neck cancer.

Objectives:

- ***Primary Objective:***
  Evaluate the feasibility and acceptability of the guided imagery intervention to reduce RT-related symptoms of anxiety and depression in patients with HNC. These data will be used to inform future grant applications.

- ***Secondary Objectives:***
  We will also collect data to evaluate the impact of a GI intervention on symptoms of anxiety and depression in patients with HNC relative to treatment as usual.

Endpoint:

- ***Primary Endpoint:***
  Acceptability and feasibility of guided imagery intervention assessed through self-reported intervention use and qualitative interviews with intervention participants

- ***Secondary Endpoints:***
  Self-reported anxiety and depression at one month after completion of radiotherapy as measured by the Hospital Anxiety and Depression Scale

- ***Tertiary/ exploratory:***
  Self-reported use of anxiolytic medications as measured by timeline follow-back methodology. We will also measure health-related quality of life in patients receiving the intervention and treatment as usual.

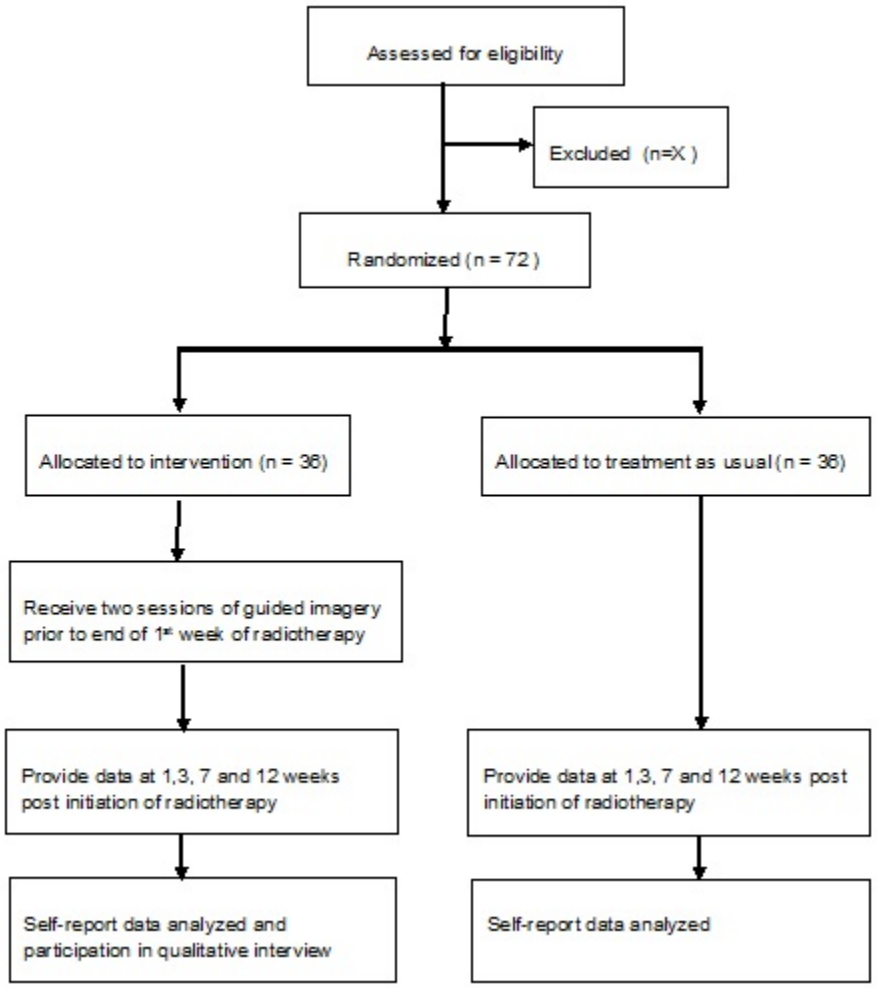
Population:

- ***Sample size***
  - *Maximum number of participants that can be enrolled is 72 (allow for screen failures)*
  - *Minimum number of participants to be enrolled 50 (number of participants needed to answer scientific question/aims)*
- ***Gender*** *Male and Female*
- ***Age Range*** *18-100*
- ***Demographic group*** *Ambulatory outpatients receiving radiotherapy for head and neck cancer*

- ***General health status*** *Initiating radiotherapy for head and neck cancer*

Number of Participating Sites enrolling participants:	*1 (University of Colorado Cancer Center)*
Description of Study Agent:	*Guided imagery*
Study Duration:	*2 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

Patients with head and neck cancer (HNC) comprise a unique population due to their high risk for treatment failure and death [1, 2], heavy symptom burden [3], and intensive treatment schedules. As a result, HNC has been labeled the "most psychologically traumatic cancer to experience." ([4], p 2) These patients are at risk for facial disfigurement and functional changes in ability to speak, breathe, eat and swallow [4-7]. As compared to patients with other cancer diagnoses, patients with HNC report high levels of psychological distress (i.e., symptoms of anxiety and depression) and social isolation [8-12], with more than half of HNC patients reporting persistent psychological distress [13]. Additionally, their risk for suicide is four times that of the general population [14]. Evidence shows that much of their distress is directly related to the treatments they undergo, including radiotherapy (RT;[8]). This is an at-risk, high needs population of cancer patients in need of an intervention for treatment-related distress.

Radiotherapy (RT), a standard treatment for head and neck cancer, is associated with high levels of psychological distress in HNC patients [8, 15]. RT involves daily treatments often for weeks at a time. Treatment begins with a "CT simulation" to determine accurate positioning while undergoing RT [16]. Prior to initiating RT, rates of clinically significant anxiety range from 20% to 47%, depending on assessment measure, and initially peak around week five of RT [8, 17-19]. Pretreatment depression tends to be lower than anxiety (15%), but increases over the course of treatment (29%) and persists post-RT [18, 20, 21].

Head and neck cancer is highly prevalent with approximately 650,000 cases diagnosed each year [22], and yet it is understudied in the field of behavioral medicine [4]. This is surprising given the high levels of psychological distress [23] which can complicate adjustment to diagnosis and treatment [6], as well as overall survival [24]. Psychological distress is a significant predictor of patient survival [25] with lower survival rates shown for cancer patients who reporting symptoms of depression (71% versus 86%) [17]. For HNC patients undergoing RT specifically, levels of depression have been associated with decreased overall survival [15]. It is critical that

these difficulties be addressed given the direct relationships found between mental health and clinical outcome.

Guided imagery (GI) is a behavioral relaxation technique involving the visualization of calming images and is considered an adjuvant cancer therapy [26]. A systematic review of GI in a heterogeneous sample of patients with cancer found positive effects on depression, anxiety and quality of life compared to patients in a control group [26]. It has been found to enhance comfort and quality of life and reduce anxiety and fatigue in women undergoing RT for breast cancer [27]. The impact of GI in patients with HNC, a highly distressed population, is unknown.

2.2 RATIONALE

Patients with head and neck cancer (HNC) comprise a unique population due to their high risk for treatment failure and death [1, 2], heavy symptom burden [3], and intensive treatment schedules. Psychological distress is a significant predictor of patient survival [25] with lower survival rates shown for cancer patients who reporting symptoms of depression (71% versus 86%) [17]. For HNC patients undergoing RT specifically, levels of depression have been associated with decreased overall survival [15]. It is critical that these difficulties be addressed given the direct relationships found between mental health and clinical outcome. The goal of this interdisciplinary pilot study is to evaluate the feasibility, acceptability and preliminary efficacy of a guided imagery intervention to reduce RT-related symptoms of anxiety and depression in patients with HNC relative to treatment as usual. The findings will be used for future grant applications to perform larger studies.

Aim 1: To assess participants' perceived acceptance and feasibility of a guided imagery intervention for radiotherapy-related (RT) anxiety and depression in head and neck cancer patients through quantitative and qualitative data collection Head and neck cancer patients receiving RT (n = 72) will be randomly assigned to a guided imagery intervention for RT-related anxiety and depression or to treatment as usual. The intervention consists of two individual, in-person or virtual (telephone or videoconference), tailored sessions that will introduce a relaxation practice prior to CT simulation and during the first week of RT, as well as identification of integration strategies into the patients' treatment plans. The treatment as usual condition involved education about treatment and access to psychosocial support available through UCCC. Semi-structured interviews with participants from the intervention arm will assess the perceived acceptance and feasibility of guided imagery for addressing symptoms of anxiety and depression related to RT. Participants will track weekly use of the guided imagery intervention during RT via time line follow-back (TLFB) methods. We hypothesize that themes will emerge from the qualitative data that will indicate general acceptance and usefulness of guided imagery.

Aim 2: Determine the impact of a guided imagery intervention for radiotherapy-related (RT) anxiety and depression in head and neck cancer patients.

We hypothesize that guided imagery will result in measured decreases in patient reported anxiety and depression as measured by the Hospital Anxiety and Depression Scale over the course of RT. Additionally, we hypothesize that guided imagery will demonstrate greater reductions in

anxiety as compared to treatment as usual. We hypothesize that symptoms of depression will remain stable, rather than increasing, over the course of RT in participants in the guided imagery arm.

Exploratory Aim 1: To engage in exploratory analyses to investigate the potential impact of guided imagery on self-reported anxiolytic use. Anxiolytic use will be assessed via participant self-report using time line follow-back methods for weekly monitoring and data regarding prescription of anxiolytic drugs in the patient's electronic medical record. We expect that participants in the guided imagery group will report lower proportions of anxiolytic utilization than the control group.

Exploratory Aim 2: To examine the impact of a guided imagery intervention on health-related quality of life and perceived symptom burden compared to treatment as usual. Participant-reported health-related quality of life and perceived symptom burden assessed by the Functional Assessment of Cancer Therapy - Head and Neck Version (FACT-HN) and symptom burden will be assessed by the Memorial Symptom Assessment Scale Short Form (MSAS-SF). We hypothesize that participants who receive the intervention will have higher health-related quality of life than participants who receive treatment as usual. We also hypothesize that symptom bother will be lower in participants who receive the guided imagery intervention compared to treatment as usual.

The successful implementation of this interdisciplinary research will result in lower psychological distress through the reduction of symptoms of anxiety and depression. This is particularly significant in a population of patients who are highly vulnerable to anxiety and depression as they undergo burdensome treatment and cope with heavy symptom burden. These psychological symptoms can influence treatment adherence and survival; thus, behavioral intervention is paramount. Guided imagery holds the potential to significantly improve distressing psychological symptoms in vulnerable patients facing intensive treatment and heavy symptom burden. This intervention will directly address psychological distress to establish preliminary efficacy that will lay the groundwork for larger efficacy and dissemination trials.

2.3 POTENTIAL RISKS AND BENEFITS

There are minimal risks to study participants. However, we will ask participants to complete measures assessing symptoms of anxiety, depression, quality of life, and symptom burden. In the case that this is upsetting, psychosocial support will be available. However, participants, particularly those who participate in the GI intervention, are expected to benefit from study participation. All participants in the study will ultimately receive the GI intervention materials. Further, the successful completion of this study will provide preliminary information about an intervention to reduce psychological distress in a vulnerable population. We strongly believe that the potential benefits of this study outweigh the risks.

2.3.1 KNOWN POTENTIAL RISKS

There are minimal risks to study participation. Participants will be asked to reflect on psychological states, which can be upsetting. All participants will have access to supportive oncology services available at the University of Colorado Cancer Center, including access to clinical psychologists and oncology social workers. All PHI will be protected by storing data in restricted access databases (REDCap).

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: Guided imagery has been helpful in reducing the severity of symptoms of anxiety and depression in patients with cancer. Therefore, we expect that the participants in our study who are randomized to the intervention condition will experience lower levels of anxiety and depressive symptomology versus participants in the treatment as usual condition.

- To Society: This is a novel clinical project with the potential for wide-ranging impact. Head and neck cancer has been labeled the "most psychologically traumatic cancer to experience." Depression and anxiety are highly prevalent in this population and can be exacerbated by cancer-directed treatment. Symptoms of depression affect immunocompetence, treatment adherence, and other aspects of health-related quality of life that persist after the treatment completion. Patients with anxiety report a greater impact of their disease including intrusive thoughts and avoidance behaviors. Yet, there is a paucity of well-designed randomized controlled trials targeting psychological distress in this population.

- Justify the importance of the knowledge gained: There are no published interventions of GI for anxiety and depression in patients with head and neck cancer despite its efficacy in other populations of patients with cancer. The goal of this intervention is ultimately to design an intervention that can be integrated into clinical care for patients with head and neck cancer.

3 OBJECTIVES AND PURPOSE

Primary objective: The goal of this interdisciplinary pilot study is to collect data to evaluate the feasibility and acceptability of the guided imagery intervention to reduce RT-related symptoms of anxiety and depression in patients with HNC. These data will be used to inform larger studies and grant applications.

Secondary objective: This study will also assess the impact of the GI intervention on symptoms of anxiety and depression in patients with HNC relative to treatment as usual

4 STUDY DESIGN AND ENDPOINTS

4.1 DESCRIPTION OF THE STUDY DESIGN

This will be a randomized controlled trial. Following consent, participants will provide baseline data including demographic and clinical characteristics. Participants will be randomized to the guided imagery intervention (delivered in-person or virtually) or to treatment as usual. Due to study design, it is not possible to blind either participants or investigators to study condition. However, the biostatistician will be blinded to participant group to minimize bias in analyzing the data. Participants will complete assessments at baseline, following initiation of RT, halfway through RT, at the end of RT, and one month after the end of RT.

4.2 STUDY ENDPOINTS

4.2.1 PRIMARY ENDPOINT

The primary endpoint of the study is the feasibility and acceptability of the guided imagery intervention for anxiety and depression related to radiotherapy. Feasibility and acceptability will be assessed following study participation through both qualitative and quantitative methods. Feasibility of intervention use will be assessed through rates of study enrollment and GI session attendance. It will also be assessed through self-reported use of the GI intervention measured through timeline follow-back. Acceptability of the intervention will be assessed through qualitative interviews with intervention participants. The interviews will assess participant experience in the intervention including thoughts about the intervention content and structure of the intervention.

4.2.2 SECONDARY ENDPOINTS

Self-reported anxiety and depression at one month after completion of RT are the secondary endpoints. This will be assessed by the Hospital Anxiety and Depression Scale. The Hospital Anxiety and Depression Scale (HADS; [28]) is a 14-item self-report measure of anxiety and depression symptoms for use in medically ill patients, as it does not include the somatic symptoms of anxiety and depression that confound the assessment of distress in medically ill patients, and has demonstrated high reliability and validity in medically ill populations [29]. The measure contains seven anxiety items and seven depression items, which correspond to two subscales (HADS-A and HADS-D). For each item, the participant is asked to identify how much a given statement is applicable (*Most of the time*, *A lot of the time*, *From time to time, Occasionally* or *Not at all*). A cut score of 8 identifies cases of anxiety and depressive disorders for each subscale, resulting in sensitivity and specificity of approximately .80 [29].

4.2.3 EXPLORATORY ENDPOINTS

Participant use of anxiolytic medications will be assessed through both medical record review of prescriptions and patient reported use. All participants will record their use of any of the following medications: alprazolam, bromazepam, chlordiazepoxide, clonazepam, clorazepate, diazepam, flurazepam, and lorazepam. All participants will be given a TLFB measure to track daily use of anxiolytics during the course of the study. This will be administered weekly via a HIPAA secure REDCap link sent to his or her email. Participants who do not complete the weekly TLFB report in REDCap will be contacted by study staff in order to administer the recall via telephone. The TLFB is a reliable measure of patient-reported substance use (i.e., cigarettes, cannabis, and alcohol). Additionally, we will assess health related quality of life using the FACT-HN and symptom burden using the MSAS-SF. These measures will be included in exploratory analyses of the impact of the intervention on health-related quality of life and the impact of symptoms. Symptom presence may be included as a potential covariate in outcome analyses.

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 consent to the study procedures.
2. Stated willingness to comply with all study procedures and be available for the duration of the study.
3. Be aged 18 – 100.

4. Ability to read and communicate in English.
5. A confirmed malignancy of the head and neck region (including metastases from other primary tumors and cancers of unknown primary).
6. Initiation of RT at the University of Colorado Cancer Center.
7. Psychiatric and cognitive stability as assessed by chart review (i.e., no documented dementia diagnosis or unmanaged psychiatric symptoms) and study personnel (i.e., ability to attend to meeting with study personnel).
8. Ability to meet remotely via internet connection or over the phone.

5.2 PARTICIPANT EXCLUSION CRITERIA

An individual who fails to meet any of the inclusion criteria will be excluded from participation in this study. Mental health providers involved in this study may also use clinical judgment regarding appropriateness of participant for study (e.g., psychiatrically unstable).

5.3 STRATEGIES FOR RECRUITMENT AND RETENTION

We will recruit approximately 72 patients at the University of Colorado Cancer Center who are initiating radiotherapy (RT) for a cancer of the head and neck. This will include patients with a confirmed malignancy of the head and neck region, from clavicle to skull. This will include patients with diagnoses that include skin, thyroid, oral cavity, pharynx, larynx, paranasal sinuses and nasal cavity, salivary glands, unknown primary and metastases from other primary tumors. Participants will be initially screened for eligibility via chart review. 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. The study research assistant will screen patients for eligibility and will communicate with the radiation charge nurse regarding patient eligibility. Dr. Studts, licensed clinical psychologists, will review questions or concerns about participant eligibility for mental health reasons. Eligible participants will be contacted for consent following their initial visit with a radiation oncologist. A study research assistant will communicate eligibility to the patient's treating radiation oncologist and obtain permission to approach from the treating physician. The study research assistant will then call the patient to assess interest via telephone. The patient can consent to study participation then or schedule a later time for consent with the research study assistant. There will be two possible routes for consent: Participants may provide verbal consent for screening and baseline procedures only and will provide a signed full consent prior to other study procedures (in person or via e-consent). The other route, participants will provide informed consent and authorization for the entirety of the study at the time of screening/baseline through an e-consent process. Signatures may be obtained via REDCap, mail, e-mail with scanned

document or picture of the signed consent, or by bringing the signed consent and authorization into the clinic.

Following consent, the participant will provide contact information to the study research assistant who will remain in contact with the participant. The research assistant will coordinate intervention and assessment sessions as necessary. Study data will be collected via email link connected to a secure REDCap database. These assessments can also be conducted in clinic via electronic tablet, or by phone if necessary. This will be coordinated by the study research assistant.

Given that patients with HNC are a highly distressed population, it is likely that some of the participants in this study will have a history of anxiety and depression as well as current symptomatology. Patients who are psychiatrically unstable or have cognitive impairment will be excluded from participation as determined by chart review and/or assessment of study personnel. All participants in the study will have access to all psychosocial supports available at UCCC including social work and clinical psychology.

All study participants will be provided with an MP3 player that they will be allowed to keep as part of study participation. Participants in the treatment as usual group will receive it at the end of study participation. Further, participants who participate in the qualitative interviews will receive at $25 gift card in compensation for their time.

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. The study investigators may terminate the participation of participants who display inappropriate or disrespectful behavior toward the study personnel.

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 previously stated, the anticipated risks of study participation are low. However, if the study personnel believe at any point that participation that study participation is detrimental to the

participant's health, participation will be suspended and the participant will be connected with mental health resources at the University of Colorado Cancer Center.

6 STUDY AGENT

6.1 STUDY AGENT(S) AND CONTROL DESCRIPTION

The study agent used in this trial is GI. GI is a relaxation technique involving the visualization of images and is considered an adjuvant cancer therapy (26). The GI intervention will include direct, written, and audio delivery of one of three GI vignettes. The patient will be able to choose one of the three vignettes. The vignettes are sourced, with permission (31) from the University of Michigan Comprehensive Cancer Center's Guided Imagery Library. The approximately twelve-minute-long vignettes included in the study will be: *Taking a Walk*, *Healthy Cell Alliance for Treatment,* and *Daily Intention* (32). Each vignette is similar in length and structure and relies on the same mechanisms of relaxation and bringing images to mind. After being randomized to the intervention participants will receive their first intervention exposure session before their scheduled CT simulation. After the initial session, the participant will be given an iPod shuffle on which their intervention material will be recorded. They will then receive a second, in person, intervention exposure during the first week of RT. The intervention, based on established psychotherapy principles, can later be self-administered both before and during RT.

A master's level therapist (i.e., psychology doctoral student, licensed clinical social worker, etc.) will deliver the GI intervention. Each study therapist will attend a training session either in person or virtually (via telephone/video conference) that will provide an introduction to the intervention, a review of each session component, and an opportunity to participate in role-play exercises to ensure facility in delivering the therapy. All training materials will be made available to the study therapists for continued review. Supervision will be provided to each study therapist as needed by Dr. Studts.

The control or treatment as usual condition will include an orientation to RT from the clinic nurse coordinator. This will include a tour of the treatment room and education about RT. Patients will also receive educational materials about RT including the process of RT and CT simulation, treatment side effects, pain management, and swallowing exercises. Participants in this condition will also have access to psychosocial support resources (i.e., clinical psychologists and social workers) at UCCC. Patient use of these services during the study period will be monitored through chart review.

7 STUDY PROCEDURES AND SCHEDULE

7.1 STUDY PROCEDURES/EVALUATIONS

Following consent and completion of baseline measures, the participant will be randomized to either the intervention or treatment as usual condition. The research study assistant will coordinate the scheduling of the two intervention sessions for participants in the GI condition. Administration of the study measures will occur online, via REDCap. Participants will be offered the opportunity to begin/complete the survey at the cancer center on a provided tablet, but may also complete the survey in its entirety at home on their own personal internet-connected device.

All participants will complete assessments at baseline, following initiation of RT (during Week 1 of treatment), approximately halfway through RT (during Week 3 of treatment), at the end of RT (during Week 7 of treatment), and one month following completion of RT (around Week 12 after beginning treatment). Patients may complete the assessments listed any time during the specified week (7 days) of treatment, with Day 1 being defined as the first day of radiation treatment. Each session will also be recorded and reviewed for fidelity to the intervention. Study measures include the following:

I. Anxiety and depression
   a. The Hospital Anxiety and Depression Scale (HADS; (33)) is a 14-item self-report measure of anxiety and depression symptoms for use in medically ill patients, as it does not include the somatic symptoms of anxiety and depression that confound the assessment of distress in medically ill patients, and has demonstrated high reliability and validity in medically ill populations (34). The measure contains seven anxiety items and seven depression items, which correspond to two subscales (anxiety and depression). For each item, the participant is asked to identify how much a given statement is applicable (*Most of the time*, *A lot of the time*, *From time to time, Occasionally* or *Not at all*). A cut score of 8 identifies cases of anxiety and depressive disorders for each subscale, resulting in sensitivity and specificity of approximately .80 (34). In a study of screening for depression in patients with head and neck cancer, the HADS demonstrated the highest absolute levels of sensitivity, specificity, and positive predictive values for identifying cases of Major and Minor Depression compared to other commonly used measures of depression [30]. It has also been found to be a useful for screening for both anxiety, depression and general psychological distress in this specific population [31].

II. Symptom burden
   a. The Memorial Symptom Assessment Scale Short Form (MSAS-SF; [32]) is a multidimensional symptom assessment instrument. It assesses both symptom presence and symptom distress. It assesses the occurrence of 26 physical symptoms and four psychological symptoms on a scale from 0 (“no symptom”) to 4 (“very much”). Distress is rated on a 5-point scale including not at all, a little bit, somewhat, quite a bit, and very much. The scale yields a total symptom distress score (TMSAS), a global distress index (GDI), a physical symptom distress score (PHYS), and a psychologic symptom distress score. (PSYCH) In a sample of patients with cancer, Cronbach alpha was 0.80 for the GDI, 0.82 for the

PHYS, and 0.76 for the PSYCH, and 0.87 for the TMSAS. It also demonstrated good criterion validity in patient with cancer.

III. Health-related quality of life
   a. The Functional Assessment of Cancer Therapy - Head and Neck Version (FACT-HN) is a 27-item self-report instrument designed to assess quality of life for patients with HNC (35). Items assess four domains: physical, social/family, emotional, and functional well-being as well as specific items assessing head and neck symptoms. The scale uses a Likert-type scale (0 to 4) to produce subscale and total scores with higher scores indicating higher quality of life. It is a reliable, valid measure of quality of life for patients with head and neck cancer (35).

IV. Intervention use
   a. Participant reported acceptance of the intervention will also be assessed via time line follow-back (TLFB; (38)). Participants will be given a TLFB measure in order to ascertain a retrospective, calendar-based, daily estimate of use of the intervention materials. This will be sent to participants via a HIPAA secure REDCap link. Study staff will contact participants who do not return their TLFB data in order to administer the recall via telephone.

V. Anxiolytic use
   a. Participant use of anxiolytic medications will be assessed through both medical record review of prescriptions and patient reported use. All participants will record their use of any of the following medications: alprazolam, bromazepam, chlordiazepoxide, clonazepam, clorazepate, diazepam, flurazepam, and lorazepam. All participants will be given a TLFB measure to track daily use of anxiolytics during the course of the study. This will be administered via a HIPAA secure REDCap link. Participants who do not return their TLFB data will be contacted by study staff in order to administer the recall via telephone. The TLFB is a reliable measure of patient-reported substance use (i.e., cigarettes, cannabis, and alcohol).

Following study participation, participants in the intervention condition will be invited to participate in a qualitative interview. The interviews will be conducted by the study investigator, Dr. Studts or by the research study assistant who will be appropriately trained in qualitative methodology. Qualitative data regarding acceptability of the intervention will be gathered through one-on-one, standardized open-ended interviews. Interviews will be conducted using a semi-structured interview protocol (37), which will be given either in person or over the telephone. The interview will be recorded, after obtaining consent to do so by the participant, so that it can be transcribed and analyzed appropriately. Interviews will last approximately 30 minutes.

7.3 STUDY SCHEDULE

7.3.1 SCREENING

Screening Visit: Day 1

The research study assistant will review medical history to determine eligibility based on inclusion/exclusion criteria prior to approaching the potential participant. Study personnel will inform the patient's treating physician and Radiation Oncology charge nurse and confirm eligibility.

Eligible participants will then be presented with study parameters.

7.3.2 ENROLLMENT/BASELINE

Enrollment: Day 1

Enrollment will generally occur on the same day as the Screening visit. However, interested patients can enroll in the study in the time between the Screening visit and CT simulation. There will be two possible routes for consent:

1. Participants may provide verbal consent for screening and baseline procedures only, and will provide a signed full consent prior to other study procedures (in person or via e-consent).
2. Informed consent and authorization for the entirety of the study will be obtained at the time of screening/baseline through an e-consent process. Signatures may be obtained via REDCap, mail, e-mail with scanned document or picture of the signed consent, or by bringing the signed consent and authorization into the clinic. All questions will be answered by the study personnel and/or treating physician

Study personnel will then complete the enrollment portion of the REDCap survey with the patient, which will include information regarding the patient's date of birth and email address. Additional information documenting the date of the informed consent as well as the consenting study personnel will also be collected.

The participant will complete study baseline measures and then will be randomized to either the intervention of treatment as usual condition. Participants may complete baseline measures any time after consenting and before the CT simulation visit.

7.3.3 FOLLOW-UP

Participants randomized to the intervention condition will complete two in-person or virtual (telephone or secure videoconference) guided imagery sessions. The first will be during the week of the CT simulation visit and the second during the first week of RT (See Table 1).

Table 1. Intervention schedule

Guided Imagery Session	Time	Session Aims
Session 1	During the week of CT simulation	• Introduction to guided imagery • Selection of guided imagery vignette • In-session delivery of vignette • Planning for use of guided imagery
Session 2	During first week of RT	• Review of guided imagery use • Selection of new vignette if necessary • Addressing barriers to guided imagery use

Patients will then be able self-administer the GI both before and during RT throughout their treatment. Follow-up data for all participants will be collected during the third week (or halfway point) of RT, following completion of RT, and approximately one month following completion of RT. All participants will complete weekly self-assessment of anxiolytic medication use. Intervention participants will complete weekly assessments of guided imagery intervention use. See Table 2 below for schedule of data collection.

Table 2. Assessment schedule for study participants

Construct	Measure	Baseline & Prior to RT	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 12
Anxiety	HADS-A	X	X		X				X	X
Depression	HADS-D	X	X		X				X	X
Symptoms	MSAS-SF	X			X				X	X
Health-related QOL	FACT-HN	X			X				X	X
Intervention use*	TLFB-I	X	X	X	X	X	X	X	X	
Anxiolytic use	TLFB-A	X	X	X	X	X	X	X	X	
Demographics		X								

* Guided imagery participants only

HADS-A = Hospital Anxiety and Depression Scale – Anxiety Subscale; HADS-D = Hospital Anxiety and Depression Scale – Depression Subscale; MSAS-SF = Memorial Symptom Assessment Scale – Short Form; FACT-HN = Functional Assessment of Cancer Therapy – Head and Neck Version; TLFB-I = timeline follow-back for intervention use; TLFB-A = timeline follow-back for anxiolytic use

7.3.4 FINAL STUDY VISIT

Following completion of the Week 12 study assessment measures the participant will connect with the study research assistant either in person or by telephone. Treatment as usual participants

will be provided with an MP3 player containing the guided imagery audio files either in person or by mail. Intervention participants will be asked to participate in a 30-minute qualitative interview assessing the acceptability and feasibility of the intervention. This visit, once scheduled, will be the final study visit.

7.3.5 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 participation. This decision will be documented by research personnel.

7.4 SCHEDULE OF EVENTS TABLE

	Screening & Enrollment	Prior to RT	During Radiation Therapy (RT)							Post-RT
	Baseline	CT Simulation Visit	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 12
Consent	X									
Eligibility[1]	X									
Demographics	X									
Randomization[2]	X									
CT Simulation		X								
In-Person or virtual GI Session		X	X							
Patient self-administered GI use[3]			X	X	X	X	X	X	X	
Anxiety HADS-A	X		X		X				X	X
Depression HADS-D	X		X		X				X	X
Symptoms MSAS-SF	X				X				X	X
Health-related QOL FACT-HN	X				X				X	X
Intervention use TLFB-I[3]		X	X	X	X	X	X	X	X	
Anxiolytic use TLFB-A		X	X	X	X	X	X	X	X	
Research Assistant Contact for F/U[4]										X
Qualitative Interview[5]										X

*Patients may complete the assessments for weeks 1, 3, 7 and 12, listed above any time during the specified week (7 days) of treatment, with Day 1 being defined as the first day of radiation treatment. TLFB measures may be completed at any time.

1. Determined by chart review and confirmation of eligibility between research study personnel and treating physician.
2. Upon completion of baseline measures.
3. Guided imagery (intervention) participants only.
4. Following completion of 12-week study measures, in person or on the phone:
   Treatment as usual participants will be provided with an MP3 player containing the guided imagery audio files either in person or by mail.
   Intervention participants will be offered the opportunity to participate in a 30-minute qualitative interview assessing the acceptability and feasibility of the intervention.
5. The qualitative interview may be conducted via phone or in person following completion of the Week 12 study assessments.

7.5 CONCOMITANT MEDICATIONS, TREATMENTS, AND PROCEDURES

All prescription medications related to the study aims taken during study participation will be recorded in the study database. For this protocol, relevant prescription medications include anxiolytic medication (i.e., alprazolam, bromazepam, chlordiazepoxide, clonazepam, clorazepate, diazepam, flurazepam, and lorazepam), antidepressant medications, sleep aids, and analgesics. These medications will be identified through chart review, and include prescription medications, over-the-counter medications, and non-prescription medications. Following study completion, the participant's medical record will be reviewed and the above medications will be identified as will the date of the prescription.

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, who is a licensed clinical psychologists and providers 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)

Adverse event means untoward or unfavorable medical occurrence related to an intervention in humans.

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 guided imagery audio recordings.

- 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. Rather this is the general course of anxiety and depression in the context of RT for HNC.

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 (i.e., participation in intervention or completion of study measures) 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

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 last day of study participation. At each study visit, the investigator will inquire about the occurrence of any related AEs 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 PI to report incidents or events that meet the criteria for UAPs reporting to their IRB using the IRB's standard UAP form. The PI is responsible for reporting the UAP to the UCCC DSMC, if applicable.

8.4.3 REPORTING OF PREGNANCY

This section is not applicable. Pregnancy will not affect the participant's eligibility or necessitate modification of study procedures.

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 activities is as follows:

• Conduct of internal audits

• Ongoing review of all serious adverse events (SAEs) and unanticipated problems (UAPs)

• May submit recommendations for corrective actions to the CU Cancer Center's Executive Committee

Per the CU Cancer Center Institutional DSM Plan, SAEs and UAPs are reported to the DSMC, IRB and the principal investigator per protocol. All SAEs and UAPs are to be reported to the DSMC within 7 (for fatal or life-threatening events) or 15 (non-life-threatening events) calendar days of the principal investigator receiving notification of the occurrence.

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.

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 feasible and acceptable.

- Secondary Efficacy Endpoint(s):

(1) The HADS-A score will be smaller in patients receiving guided imagery intervention compared to controls (whose score should remain unchanged from baseline), and (2) the HADS-D score will be smaller in the guided imagery group compared to controls (whose HADS-D should increase over baseline)

10.2 ANALYSIS DATASETS

The dataset will consist of demographic and clinical information from the participant's medical chart. It will also include the self-reported data provided by study participants.

10.3 DESCRIPTION OF STATISTICAL METHODS

10.3.1 GENERAL APPROACH

Study Co-Investigator and biostatistician, Kathleen Torkko, PhD, will conduct the analysis of the primary endpoint. Dr. Studts will conduct the analysis of the secondary endpoint using ATLAS.ti.

10.3.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

The purpose of the qualitative data analysis, which will address the secondary aim of this project, is an in-depth understanding of patient's acceptance and perceived usefulness of the guided imagery and music therapy interventions for addressing anxiety and distress related to radiation therapy. 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 (39). This is an inductive approach to data analysis through which each piece of data (e.g., statements, emerging themes, etc.) is compared to other pieces of data and evaluated for similarities and/or differences. In qualitative research, it is generally accepted that data collection continues until "saturation" had been met. 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, from studies that utilize individualized interviews to develop and understand nuances of theory, that between 12-30 participants are typically needed to reach saturation (40).

10.3.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

The study investigators will use independent sample t-tests at the end of radiation treatment (RT) to test the hypotheses (1) the HADS-A score will be smaller in patients receiving guided imagery intervention compared to controls (whose score should remain unchanged from baseline), and (2) the HADS-D score will be smaller in the guided imagery group compared to controls (whose

HADS-D should increase over baseline). The study is powered to test these hypotheses. Additionally, we will analyze the data using repeated measures analyses or mixed models to study changes over time and to test for interactions between time and treatment groups.

10.3.4 ADHERENCE AND RETENTION ANALYSES

Given that the feasibility of recruitment, enrollment, and completion of the study are secondary objectives of this project, we will evaluate study retention. Specifically, analyses will evaluate the number of participants approached, the number consented, the number who access the REDCap Survey, and the number who complete the survey. Study personnel will attempt to contact persons who failed to complete the study to ask why they dropped out. Data gathered will be used to inform future studies and grant applications.

10.3.6 TABULATION OF INDIVIDUAL RESPONSE DATA

Individual data will be entered into REDCap using a unique study identification number.

10.3.7 EXPLORATORY ANALYSES

The study investigators will use descriptive statistics (i.e., proportions of people at each time point) to examine differences in anxiolytic use between treatment groups. At the end of RT, a chi-square or Fisher's exact test will be used to determine if there is a difference in the proportion of people using anxiolytics by treatment group.

10.4 SAMPLE SIZE

We expect that we will be able to enroll up to 72 patients who will be randomized into either control (n=36) or guided imagery intervention (n=36). Based on a published study looking at HADS scores in HNC patients receiving RT (20), we used the values for means and standard deviations (SD) from that study for our control group. We also determined that SD would be known and equal. Significance levels (alpha) are set at 0.05 for a two-sided independent-sample equal-variance t-test. For the HADS-A hypothesis, the mean score in controls at the end of RT was 6.9 (SD = 5.0). With group sample sizes of 36 and 36, we will have 80% power to reject the null hypothesis of equal means when the HADS-A score in the guided imagery group is ≤ 3.6 (a $\geq$48% difference between the scores for each group at the end of RT). For the HADS-D hypothesis, the mean score in controls at the end of RT was 11.2 (SD=5.5). Group sample sizes of 36 and 36 achieve 80% power to reject the null hypothesis of equal means when HADS-D score in the guided imagery group is ≤ 7.5 (a $\geq$33% difference between the scores at the end of RT). Although we can achieve reasonable power to detect clinically significant differences

between our study groups, the main goal of this study is to determine the feasibility of a larger study. As such, the results of our analyses are not meant to answer the question of the effectiveness of our intervention, but to provide preliminary data for a larger grant application.

10.5 MEASURES TO MINIMIZE BIAS

10.5.1 ENROLLMENT/ RANDOMIZATION/ MASKING PROCEDURES

The REDCap randomization tool will be used to facilitate randomization. Dr. Torkko will create random allocation tables that she will either upload into the REDCap project or will provide to the REDCap Administrator to be uploaded. Dr. Torkko will generate the random allocation tables according to study design specifications as determined by the statistician and investigator/s. Participants will be randomized when the research study assistant or study investigator enter a participant's REDCap record and click the "Randomize" button. Clicking this button triggers REDCap to check the allocation table and display the group to which the participant should be randomly assigned. This assignment is permanent and not editable within the participant record and, like all other activity within REDCap, is tracked and not modifiable in the audit log.

11 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Appropriate research records will be maintained as necessary; however, all data collection will occur via REDCap, so it is likely any creation of source documents will be minimal.

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. ICH E6 may also be followed to the extent it has been adopted by and is in accordance with OHRP 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 agent, study procedures, and risks are given to the participant and written documentation of informed consent, or documentation of e-consent is required prior to starting intervention.

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 be asked to read and review the document. 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 written consent

form and ask questions prior to providing consent. The participants will have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate Participants may provide verbal consent for screening and baseline procedures only and must provide a signed full consent prior to other study procedures (in person or via e-consent). The other route, participants will provide informed consent and authorization for the entirety of the study at the time of screening/baseline through an e-consent process. Signatures may be obtained via REDCap, mail, e-mail with scanned document or picture of the signed consent, or by bringing the signed consent and authorization into the clinic.

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 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 study closure per HIPAA regulations. 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.

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.

If patients do not complete surveys or if patients complete surveys out of window in cases where the study team sent the forms appropriately, these events will not be considered protocol deviations.

15 STUDY ADMINISTRATION

15.1 STUDY LEADERSHIP

Study leadership will include the investigator, Jamie L. Studts, PhD. These co-investigators will govern conduct of the study. The co-investigators will meet in person at least monthly. Co-investigators Sana Karam MD and Kathleen Torkko PhD will provide consultation on the conduct of the study and will be in contact with Dr. Studts monthly.

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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