Study Number: CASE 4Y19
Study Title: Building Family Caregiver Skills Using a Simulation-Based Intervention for Care of Patients with Cancer

GRANT PRINCIPAL INVESTIGATOR: Susan R. Mazanec, PhD, RN, AOCN
Assistant Professor, School of Nursing, CWRU
Nurse Scientist, University Hospitals Seidman Cancer Center
2120 Cornell Rd.
Cleveland, OH 44106-4904
[redacted]

UH SITE PRINCIPAL INVESTIGATOR: Jennifer A. Dorth, MD
Assistant Professor, Radiation Oncology, CWRU
[redacted]

METROHEALTH SITE PRINCIPAL INVESTIGATOR: Suzanne Russo, MD
Physician, Radiation Oncology, MetroHealth
[redacted]

CO-INVESTIGATORS:

Celeste Alfes, DNP
Associate Professor, School of Nursing, CWRU
[redacted]

Barbara J. Daly, PhD, RN, FAAN
Professor Emeritus, School of Nursing, CWRU
[redacted]

Christine Horvat Davey, PhD, BSPS, RN
Assistant Professor, School of Nursing, CWRU
[redacted]

Nicholas K. Schiltz, PhD
Assistant Professor, School of Nursing, CWRU
[redacted]

Rod Rezaee, MD, FACS
Director, Head & Neck Reconstructive Surgery

Seidman Cancer Center, University Hospitals Case Medical Center
[redacted]

Kate Sandstrom, RN, MSN, APRN-BC, AOCN
Nurse Practitioner, Radiation Oncology
Seidman Cancer Center, University Hospitals Case Medical Center
[redacted]

Ethan (Mendel) Singer, PhD
Associate Professor, Department of Population and Quantitative Sciences, CWRU
[redacted]

Research Personnel:	To be named
Study Site(s):	University Hospitals and Satellites MetroHealth Cancer Center
Protocol Version:	2.1
Protocol Date:	2/13/2025
Sponsor:	Case Comprehensive Cancer Center
Funding Sponsor:	National Cancer Institute (1R37CA240707-01)

SUMMARY OF CHANGES

Please provide a list of changes from the previous approved version of the protocol starting at IRB approval. This table will remain blank until initial IRB approval. The list shall be a brief overview. When appropriate, a brief justification for the change should be included. This is a running list for the life of the study.

Protocol Date	Section	Change
		Initial IRB approval
		Summarize changes to first protocol amendment
10/31/19	5.2	Adding the Caregiver Reaction Assessment tool
10/31/19	5.4	Adding email REDCap surveys as an option to subjects
10/31/19	5.5	Increasing incentives for subjects
10/31/19	5.6	Updated reaction management and protection against risk section
12/5/19	Co-Is	Removed Ming Li as Co-I/Statistician and added Nicholas Schiltz
12/5/19	5.3	Interventionists will offer flashlights to caregivers during simulation
1/21/20	5.3	Removed question about caregiver missing work/activities
1/21/20	5.6	Removed study calendars and thank-you cards for participants
3/2/20	3.0	Amended eligibility to include stage IVa esophageal patients
3/26/20	3.0	Removed patient inclusion criterion "receiving first course of radiation therapy"
5/28/20	Co-Is	Min Yao added as a Co-I
5/28/20	4.0	Consent to be obtained remotely by phone or Redcap during COVID-19
5/28/20	5.3	Intervention sessions 2 & 3 delivered by phone during COVID-19
5/28/20	5.63	Symptom screening and masking for COVID-19 symptoms
7/23/20	4.0	Opt-out period for remote consent changed to 2 days
7/23/20	4.0	In-person consent will be used if remote consent is not feasible
10/2/20	4.0	Removed unique identifying code from remote consent process
12/4/20	5.3	Expanded time period for intervention session 2 to 3rd-4th week of XRT
2/23/21	5.3	Expanded time period for intervention session 1 to first 10 days of XRT
2/23/21	5.53	Added letter reminder between T3 and T4 surveys
12/6/21	3.0	Amended eligibility for NSCLC to include stage II (excluding SBRT)
1/5/22	Co-Is	Min Yao removed as a Co-I
4/5/22	5.2, 5.3	Added COST-FACIT, MOS Social Support, and Health insurance surveys
12/1/22	Co-Is, 1.0, 2.0, 3.0, 4.0, 5.1, 5.4, 5.54, 6.1	Extension protocol changes: added Cheryl Killion, MetroHealth, increased sample size, qualitative interviews, and analysis for new sub-aims.
6/11/24	Co-Is	Removed Cheryl Killion and added Christine Horvat Davey
3/13/25	PIs	Removed Dr. Peter Laye and added Dr. Suzanne Russo

TABLE OF CONTENTS

1.0 INTRODUCTION....6
1.1 Overview....6
1.2 Background and Rationale....6

2.0 OBJECTIVES....13

3.0 RESEARCH SUBJECT SELECTION....13

4.0 RESEARCH SUBJECT ENTRY....15

5.0 STUDY DESIGN AND METHODS....17
5.1 Design/Study Type....17
5.2 Selection of Instruments....17
5.3 Description of Intervention....20
5.4 Data Collection....22
5.5 Description of Study Process....24
5.6 Adverse Reactions and Their Management....25

6.0 STATISTICAL ANALYSIS....27

7.0 REFERENCES....31

8.0 APPENDICES....38

INTRODUCTION

1.1 Overview

Patients with head and neck, lung, esophageal, rectal, and anal cancers typically undergo rigorous, intense, combined-modality treatment (radiation, surgery, and/or chemotherapy) and experience high symptom burden, functional impairment, and complex psychosocial issues. Positive treatment outcomes and avoidance of complications are dependent to a large extent on the adequacy of care provided by family members. However, family caregivers (CGs) report feeling unprepared to assume the multiple, complex tasks of caregiving, including tangible help with tracheostomy care, tube feedings, wound and colostomy care, pain management, and ongoing emotional support. Despite being a critical extension of the oncology healthcare team, training of CGs to manage symptoms, deal with communication issues with the care recipients, and take care of their own physical and emotional health as CGs, is not integrated into clinical practice. The proposed study will measure the effect of a psychoeducational and skills training intervention that incorporates structured simulation or experiential learning to improve CG, patient, and healthcare utilization outcomes. We know that simulation is effective in training healthcare professionals, but little is known about its effectiveness in training family CGs. The intervention is designed for the period of active cancer treatment and the immediate transition to posttreatment survivorship, a time when the CG and patient are most vulnerable. The specific aims of this 2-group, prospective, randomized controlled trial are to: (1) evaluate the effect of a CG intervention, as compared to a control group, on CG primary (anxiety) and secondary (depression, health-related quality of life [HRQOL], and fatigue) outcomes; (2) measure the effect of the intervention on patient outcomes (HRQOL and interrupted treatment course) and healthcare utilization outcomes (unplanned hospital admission, unplanned emergency room visits, and unplanned use of intravenous fluids); (3) determine if CG self-efficacy mediates the effect of the intervention on CG anxiety; (4) determine if patient illness factors, care demands, and patient and CG demographic factors moderate the relationship between the intervention and CG outcomes; and (5) compare the costs of healthcare utilization between the intervention and control groups. We will recruit 244 CGs from University Hospitals Seidman Cancer Center at the Case Comprehensive Cancer Center and MetroHealth Cancer Center. The intervention involves three in-person, one-on-one sessions during radiation treatments, followed by a telephone contact 2 weeks posttreatment. Data will be collected at baseline, at the end of radiation treatment, and 4 and 20 weeks postradiation treatment.

The analysis will consist of linear mixed model repeated measures, mediation and moderation tests, and regression methods. The proposed project addresses NCI's Division of Cancer Control and Population Sciences mission of improving the delivery of care to individuals and family members affected by cancer. The study findings will provide crucial information for translating the psychoeducational and simulation methods used in this intervention to other CG populations and clinical settings. This study is funded by the National Cancer Institute (1R37CA240707-01).

1.2 Background and Rationale

Many of the estimated 321,000 individuals who will be diagnosed with cancer of the head and neck (HNC), esophagus, rectum, anus, and lung (non-small cell lung cancer) in the United States this year[17] will undergo rigorous cancer treatment. Although symptom profiles vary with specific cancers and treatments, patients undergoing radiation therapy experience a high symptom burden associated with significant functional impairment that will persist for months after treatment. Key members of the investigative team (Mazanec, Sandstrom, Daly) have recently completed a longitudinal descriptive study of 60 patients undergoing radiation treatment for newly diagnosed **HNC**.[18] Quality of life at the end of treatment was significantly lower than baseline ($p < .001$) and low scores persisted after treatment, with some recovery by 12 months. Anxiety improved with time, but fatigue did not. Other studies support our

finding that recovery during the first month after radiation treatment for HNC is both physically and emotionally challenging for patients due to persistent severe symptoms and lack of practical support and contact with the healthcare team.[19-22]

Similarly, patients receiving radiotherapy for **esophageal cancer** (with or without chemotherapy) will typically have improvement in dysphagia, but prolonged nutritional problems (anorexia, dry mouth, taste changes), pain, and fatigue will persist into the posttreatment survivorship period. A prospective study of patients during definitive chemoradiotherapy for esophageal cancer reported that HRQOL steadily worsened during treatment, reaching its lowest point at 12 weeks after beginning treatment.[23]

Chemoradiotherapy for patients with **advanced stage non-small cell lung cancer (NSCLC)** is associated with multiple treatment-related symptoms, including acute grade 3 to 4 esophageal toxicity, which can cause pain, dehydration, and dyshphagia.[24] Fatigue, weakness, appetite loss, altered taste, nausea, and vomiting were identified as common co-occurring symptoms (symptom cluster) persisting from diagnosis to six months later in patients with lung cancer.[25] The high symptom burden and poor performance status in patients with NSCLC is negatively associated with quality of life.[26]

Patients treated with chemoradiotherapy for **anal cancer** commonly experience severe skin reactions during treatment (radiation dermatitis and moist desquamation), as well as pain, fatigue, bowel dysfunction (fecal leakage, flatulence, frequency), urinary frequency and dysuria, and sexual dysfunction.[27] In one study, a pattern of deterioration of HRQOL and worsening symptoms by the end of radiation treatment was followed by some recovery 3 months posttreatment.[28] However, surveys of long term, colostomy-free survivors reveal common, persistent issues with bowel functioning and sexual dysfunction that are highly distressing.[29,30]

Toxicities during radiation therapy for **rectal cancer**, with or without chemotherapy, include bowel dysfunction (fecal leakage, soiling, frequency), proctitis, urinary incontinence, fatigue, skin irritation, and sexual dysfunction.[31] Rectal problems, bowel management issues, and psychosocial distress persist into early survivorship, regardless of ostomy status,[32] and often require lifestyle modifications, including use of medications, dietary changes, use of pads, and reduction of social activities.[33,34]

Family CG training and support are needed to help patients manage and cope with these intense treatment side effects that are often more severe than other cancers commonly treated with radiation (e.g., breast, prostate). The impact on the CG is long-term as recovery from treatment is prolonged, with persistent treatment and disease effects lasting years, well into survivorship for some patients.[30,32,35-37] **Patients with HNC, lung, esophageal, rectal, and anal cancer have unique care needs that are not addressed by general caregiver interventions. Interventions for these CGs must include specific technical and communication skills training, support for distress management, and education regarding caring for their own physical health.** Demands on family CGs are substantial and often include quickly gaining **new knowledge and technical skills** to manage treatment side effects, medications, nutritional supplements, ostomies, and tracheostomy and gastrostomy tubes. Yet, in two studies of CGs of patients with mixed cancer diagnoses, up to 58 percent of CGs reported unmet training needs.[6,38] Authors of a systematic review of randomized trials involving mostly CGs of patients with breast and prostate cancer found evidence that the CG interventions improved patient outcomes of pain and symptom management.[16] The authors recommended tailored, skill-based interventions that target specific patient populations to increase the effectiveness of interventions on patient outcomes. Our intervention will address this gap in the scientific literature.

Beyond the hands-on care, CGs must communicate with the patient, family, and healthcare providers about the illness. **Communication skill building** is essential to reduce "communication burden" in cancer family CGs, recently described as the CG's perceived communication challenges, such as initiating discussions, sharing emotions and feelings, and providing information with others about the patient's cancer.[39] There is high potential for communication burden in CGs of individuals

with HNC, lung, rectal, anal, and esophageal cancer, as they must adapt to an often dramatically altered lifestyle and changing roles within the family.[40-43] There is strong support in the literature for inclusion of communication skills training into CG interventions for colorectal and lung cancers,[44-47] and although there are fewer studies focused on the specific communication needs of HNC, anal, and esophageal CGs, there is support for CG communication skills training in advanced cancer.[47,48]

Although the literature describing the needs and experience of CGs of individuals with HNC, lung, esophageal, rectal, and anal cancer is limited, it is clear that the early phase of the cancer trajectory, within the first 6 to 12 months following diagnosis, is a significant time of stress for CGs.[49,50] Later-stage disease and higher symptom burden, which is common with these cancers, are associated with increased CG psychological distress.[51] Studies specific to HNC CGs underscore the severity of psychological problems: CGs have significantly higher levels of anxiety than the patients during treatment,[52] 40% can be classified as having a clinical anxiety disorder,[49] and approximately 15% have a depressive disorder.[53] It is essential to intervene with CGs early in the care trajectory, particularly during the treatment phase, to offer **psychological support**[54] and to prepare them for dealing with acute toxicities of treatment and the unique difficulties associated with these cancers. CGs have multiple unmet supportive care needs, most often related to fears of the patient's decline, concerns about recurrence, and feelings about death and dying.[55]

There are critical gaps in attending to CG emotional and psychological needs, which may have a direct influence on the psychological health of the patient. There is strong evidence that the patient-CG dyad is a relational system and that the mood states of the patient and CG are interrelated.[10,56] In a study of newly diagnosed dyads, greater CG anxiety symptoms were concurrently associated with both CG and patient depressive symptoms.[11] A CG's psychological state may also have potential for negative downstream effects on **CG physical health**.[57] Proactive interventions that teach CGs skills for caregiving tasks, as well as for communication and management of their own psychological and physical health, are needed.

Although the empirical literature underscores the need for development of interventions that provide not only skills training, but also strategies to reduce distress *early* in the treatment trajectory, there are very few studies of interventions that target CGs of individuals with HNC, rectal, anal, and esophageal cancer during the active treatment period. Studies of training interventions specific to CGs of patients with lung cancer are limited and have focused on coping skills,[58,59] communication skills,[47] and symptom management.[60] These studies were delivered online[58,59] or via telephone,[47,60] and did not focus specifically on the active treatment phase of the illness trajectory. **Our proposal fills this critical gap by testing a pragmatic intervention for CGs during radiation treatments that was developed by a multidisciplinary team of clinicians. The proposed project is a randomized controlled trial (RCT) of a psychoeducational, skills training intervention that will incorporate simulation experiences to improve CG self-efficacy for caregiving, including both technical and communication skills, as well as caring for oneself as a CG.**

Simulation, which is commonly and effectively used in education of health professionals, is a student-centered, active learning technique that uses high- or low-fidelity manikins and/or standardized patients to provide clinical activities that mimic real clinical practice.[14] Learners can practice skills in a controlled setting and receive immediate feedback. Rarely used with family CGs, simulation has been shown to be effective in training parents of chronically ill children to manage seizures,[61] home ventilators,[62] and diabetes.[63] Communication skills training for family CGs, most often noted in the dementia care literature, includes both didactic and role-play teaching methods and has been shown to be effective in improving CG communication skills, competencies, and knowledge.[64] In our study, simulation scenarios will also be used to discuss plans to overcome barriers to practicing healthful behaviors during the demands of caregiving. We know from our previous study that family CGs have

strong intentions to engage in health-promoting behaviors during cancer treatment, but report actually making behavior changes to a lesser degree.[65] Coping planning is a strategy used to anticipate and overcome barriers to enacting behavioral intentions and has been used effectively in studies of patients with coronary heart disease.[66,67]

Only two studies were found that tested a simulation or experiential intervention with cancer CGs. In a study of simulation use with HNC CGs, a one-hour, group-format tracheostomy education class that used an anatomical trainer was effective in reducing anxiety in family CGs.[68] In another study, cancer CG training with an experiential learning component delivered in a single session in the inpatient setting was effective in producing short-term improvement in self-efficacy for managing patient symptoms and CG stress.[69] Our study differs from these studies in that the intervention is delivered in individual, private sessions with the CG in the practice setting; is tailored to the specific needs associated with each cancer type; is offered over the weeks of active treatment, allowing for real-time (point-of-care) attention to CG learning needs; and incorporates simulations for both technical and communication skills training with psychoeducational strategies.

In summary, CGs of individuals with HNC, NSCLC, rectal, anal, and esophageal cancer experience unique challenges in providing care due to intense and persistent treatment side effects. The proposed CG intervention, which uses technical, communication, and health-promoting simulation strategies, aims to bolster CG skills and support during radiation therapy to improve both patient and CG outcomes.

Theoretical Framework

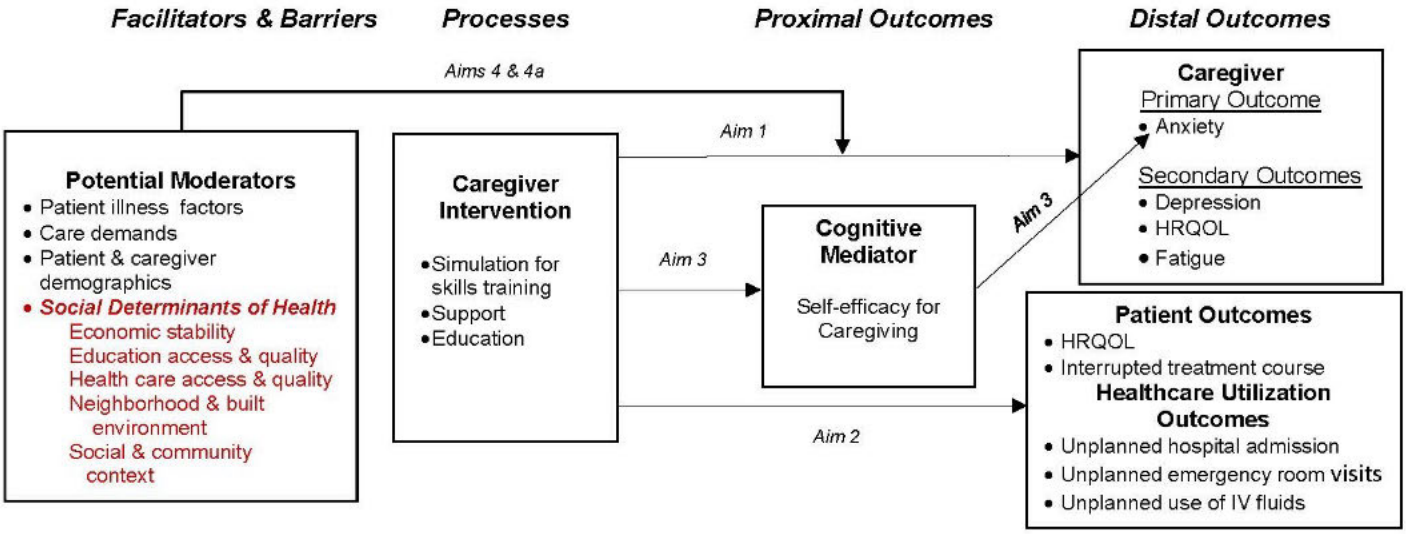
Basis for Design of Intervention. The intervention was devised based on self-efficacy, a key concept of Social Cognitive Theory. Perceived self-efficacy is the belief that one can successfully perform a specific behavior to produce an expected outcome, and according to Bandura, stronger self-efficacy beliefs can result in greater coping efforts to overcome challenging or threatening activities.[70] CG self-efficacy has implications for both the patient and CG. In a study of 152 dyads of patients with lung cancer and their family CGs, lower levels of CG self-efficacy for pain and symptom management was significantly associated with higher levels of CG strain and mood disturbance, as well as higher levels of patient-reported pain, fatigue, anxiety, and depression, and lower levels of patient-reported quality of life.[71] The proposed intervention components use strategies to strengthen self-efficacy for caregiving and self-care through *vicarious experience* (observing nurse modeling behavior during simulation), *performance accomplishments* (repeated simulation practice sessions), *verbal persuasion* (supportive nurse communication during intervention), and attention to the CG's *emotional state* (screening and intervention for emotional distress).

Basis for Study Model. The recently revised Self- and Family Management Framework,[15] which acknowledges the integral role of family in managing a chronic condition, guided the conceptualization and design of this research. The framework identifies three broad **self-management processes** of "focusing on illness needs," "activating resources," and "living with the condition." These processes are influenced by a complex array of **facilitators and barriers** at the individual, family, community, and healthcare system levels. The processes lead to **proximal outcomes** such as behaviors, cognitions, biomarkers, and symptom management. These proximal outcomes are mediators of more **distal outcomes** of self-management (health status, quality of life, psychosocial status, and health care). The proposed intervention specifically focuses on one component of this framework by targeting the processes for family CGs to increase self-efficacy, a cognitive proximal outcome, and to impact more distal CG outcomes.

The study model is shown in Figure 1. We posit that the intervention will work directly and indirectly (through self-efficacy) on CG outcomes. CG self-efficacy in this study is conceptualized as having two

components: (1) performing the caregiving role, and (2) caring for one's own health. **We hypothesize that CGs in the intervention group will show significantly greater reductions in anxiety, depression, and fatigue, and significantly greater improvements in HRQOL than subjects in the control group. We also hypothesize that the intervention will improve CG skills and ability to solve problems, resulting in greater improvements in patient HRQOL and fewer interrupted treatment courses, unplanned admissions, unplanned emergency room visits, and unplanned use of IV fluids than those experienced by patients in the control group.**

Figure 2
Revised Study Model and Related Aims



For this study, all patients (regardless of diagnosis or treatment course) have documented high symptom burden associated with significant functional impairment.[18,23,27,31] Their CGs also face similar challenges in coping with their loved ones' intense physical treatment side effects (e.g., skin breakdown, nutritional/hydration issues), and mental health issues. However, in order to account for differences due to population diversity and the potential influences on outcomes, we will track and use as covariates (potential moderators) several **patient illness factors** (variables) most relevant to the population and the outcomes of interest. These include cancer stage, time since diagnosis, treatment type (chemoradiotherapy versus radiotherapy alone), HPV status (in HNC and anal cancer), palliative care use, and patient performance status. C**are demands,** defined as hours/week spent caregiving, **patient and CG demographic characteristics** (race, marital status, employment status, socioeconomic status), and **use of mental health interventions** (support group participation, social work and/or psychologist involvement) will be assessed as covariates.

The outcomes were chosen because they are salient issues for CGs and may directly influence the CG's ability to support and care for the patient. In a study of 436 CGs of individuals with various cancer diagnoses, the prevalence of borderline/clinical **anxiety** was 36% at 6 months and 31% at 12 months post-diagnosis.[8] Borderline/clinical **depression** was reported by 15% and 16% at 6 and 12 months, respectively. Anxiety was chosen as the primary CG outcome, as opposed to depression, because it is more prevalent in CGs than depression, especially early in the care trajectory.[8,11] **Fatigue** is a common and debilitating problem for CGs.[72] ***HRQOL*** is a multidimensional, subjective, and dynamic construct reflecting an individual's satisfaction with physical, social, emotional, functional, and spiritual dimensions of life as impacted by one's health.[73]

Patient outcomes will focus on HRQOL and treatment interruption, defined as the total number of days missed due to patient or CG reasons. Treatment interruptions in radiation therapy

can negatively impact patient survival and local-regional control of the tumor,[74] and are particularly significant for patients with HNC and rectal cancer.[75-77] CG interventions are effective in improving CG well-being,[2] and more specifically, CGs who receive skill training have more confidence and experience less burden.[38] A knowledgeable, confident, and less stressed CG will be better able to deal with the physical (e.g., pain due to mucositis), emotional (e.g., depression), and social factors (e.g., lack of transportation) that may cause a patient to miss treatment.

Healthcare utilization outcomes include unplanned hospital admission, unplanned emergency room visits, and unplanned IV fluid use for treatment of dehydration. **We will evaluate costs associated with these outcomes.** Patients with HNC, NSCLC, rectal, anal, and esophageal cancer typically experience multiple toxicities during treatment. In a recent study of 63 elderly patients undergoing radiation therapy (14% with HNC, 6% with lung, 5% with rectal cancer), unplanned hospital admissions were most often related to treatment-induced toxicities, rather than frailty score, age, or functional status.[78] Trained and engaged CGs will be able to adequately manage symptoms, promote fluid and nutritional intake, and recognize situations, such as dehydration or pain, that should be brought to the attention of the healthcare team, thereby preventing unplanned admissions, emergency room visits, or need for IV fluids.

Preliminary Studies

Building on an extensive clinical background, the PI, as an early-stage investigator, has established the foundation for this study through her research on the immediate postcancer treatment transition as a multidimensional phenomenon that includes symptom management, CG and patient activation, quality of life, and interventions to reduce distress and promote self-management.

Pilot study of proposed research. In order to evaluate the feasibility and acceptability of the intervention in the current proposal, we elected to focus on one population with significant CG needs─HNC caregivers. ***Building Family CG Skills Using a Simulation-Based Intervention for Care of Patients with Head and Neck Cancer*** (Mazanec, PI), which was completed in February 2017, was conducted in the clinical setting where the intervention would be implemented. We approached 30 CGs of patients with HNC and enrolled 18, for a consent rate of 60%. Two CGs dropped out of the study. The CG who dropped from the intervention group cited scheduling and work issues. Participants were randomized to intervention (n = 8) and control (n = 8) groups and completed measures of self-efficacy, HRQOL, anxiety, and depression. Healthcare utilization outcomes were also measured. While underpowered for statistical significance, trends for the intervention group were in the hypothesized direction for self-efficacy, global physical health, anxiety, unplanned hospital admissions, and interrupted treatment course. The intervention was acceptable to both CGs and the radiation nurse who delivered the intervention. At exit interviews of 5 CGs, all rated their satisfaction with the intervention as "high." All CGs rated the communication simulations as "very helpful" and some commented on how closely the simulations mirrored their reality at home. The skills simulations with manikins were also rated highly, as "very helpful" to "somewhat helpful."

Based on the feasibility and fidelity data, as well as input from the clinicians, we have made several refinements to the intervention. First, we retained the content of the intervention, but reduced the number of in-person sessions to three in response to CG feedback. Second, we eliminated the optional telephone format of the sessions, as CGs liked the one-on-one interaction with the nurse and being able to talk about how they were feeling, including their frustrations and feelings of guilt. As is common in pragmatic trials, we will continue to allow the nurse interventionist some flexibility in adapting technical simulations to the specific needs of the CG. Having conducted this small pilot to establish feasibility and

confirm hypothesized effects, we will now expand this intervention to other diagnoses that are similarly associated with significant symptom burden, CG needs, and patient adverse effects.

Table 1. Outcome Variables in Pilot Study

	Intervention (n = 7)[a]
	Mean (SD)
CG Self-efficacy (Total Score)	
Baseline	**143.0 (23.5)**
4 weeks after RT	**146.4 (24.1)**
CG Self-efficacy for managing medical information	
Baseline	23.1 (2.0)
4 weeks after RT	23.6 (2.9)
CG Self-efficacy for caring for the care recipient	
Baseline	**47.9 (4.3)**
4 weeks after RT	**50.6 (3.6)**
CG Self-efficacy for caring for oneself	
Baseline	**31.4 (9.1)**
4 weeks after RT	**33.1 (8.6)**
CG Self-efficacy for managing difficult situations	
Baseline	40.6 (9.6)
4 weeks after RT	39.1 (11.5)
Global Mental Health (Tscore)	
Baseline	49.4 (6.6)
4 weeks after RT	49.8 (4.9)
Global Physical Health (Tscore)	
Baseline	**44.9 (8.2)**
4 weeks after RT	**46.9 (6.3)**
Anxiety (Tscore)	
Baseline	**57.8 (9.5)**
4 weeks after RT	**53.4 (11.3)**
Depression (Tscore)	
Baseline	51.3 (8.3)
4 weeks after RT	53.9 (4.7)
Unplanned hospital admissions	**2 patients**
Interrupted radiation therapy	**0 patients**

[a]One CG did not return surveys at 4 weeks and was dropped from the analysis.

Quality of Life and Perceived Health-Related Needs for Survivorship in Patients Receiving Radiation Treatment for Head and Neck Cancer (Sandstrom, PI; Mazanec, Co-I; Daly, Co-I) was a longitudinal, descriptive study of 60 patients undergoing radiation treatment for newly diagnosed HNC through the first year posttreatment.[18] Mixed random intercept longitudinal models determined that on average, HRQOL, measured by the University of Washington Quality of Life (UW-QOL) Questionnaire,[83] is 24.74 points lower ($p < .0001$) at treatment compared to baseline and 14.16 points lower ($p < .0001$) at the first month after treatment compared to baseline. The pattern of QOL trajectories confirms the need for early intervention during treatment and for continued CG support and training through the month after completion of treatment. The results of this study informed the HNC educational content and timing of the intervention to correspond to patient's experience.

CG Studies. Several of our CG studies informed the current proposal. ***A Pilot Study of Health Behaviors in Family Members of Patients with Cancer*** (Mazanec, PI) used a cross-sectional design to survey 50 patients with mixed cancer diagnoses and 39 family members (enrollment rates of 75% and 78%, respectively) at the completion of definitive treatment.[65] Results confirmed that this posttreatment transition is a "teachable moment" for family members, as CGs in the study reported low levels of physical activity, yet thought about making health behavior changes, expressed strong intentions for engaging in physical activity, and were receptive to talking with a nurse about their physical and emotional health. CGs had higher distress levels than patients at the completion of treatment ($U = 724.5$, $z = -1.95$, $p = .05$). Stress and emotional concerns were the most frequently reported barriers to improving CG health. The results identified the need for a self-care aspect to the intervention and support the need to target CG distress during treatment.

Study of Health Management in Patients and CGs During Cancer Treatment (Mazanec, PI) was a descriptive, longitudinal study of activation in 42 CGs and 62 patients newly diagnosed with colorectal cancer.[84] Using linear mixed-effects models, we found that lower CG self-efficacy for managing one's own health was associated with higher levels of CG depression ($p = .003$) and anxiety ($p = .021$), as well as higher levels of patient symptom distress ($p = .046$). As a result of this study, we designed the intervention to include an assessment of CG emotional distress during the initial few minutes of each

contact with the subject. This study also gave us operational experience in enrollment procedures and data collection in the clinical setting.

Intervention research. The proposed study builds on the team's previous investigations targeting CGs and testing interventions. Recently completed, ***Family-Centered Intervention for the Transition to Living with Multiple Myeloma as a Chronic Illness*** (Mazanec, PI) was a randomized pilot test of a CG and patient intervention for distress management within the first year after diagnosis.[85] This study demonstrates the PI's ability to implement CG interventions during the acute treatment phase. Observations made during this study of the intensity of CG concerns contributed to our decision to focus our intervention solely on the family CG, rather than take a dyadic, patient and CG approach.

2.0 OBJECTIVES

The aims of this 2-group, prospective, randomized controlled design are:
Aim 1: Evaluate the effect of a CG intervention, as compared to a control group, on CG primary (anxiety) and secondary (depression, HRQOL, and fatigue) outcomes.
Aim 2: Measure the effect of the intervention, as compared to a control group, on patient outcomes (HRQOL and interrupted treatment course), and healthcare utilization outcomes (unplanned hospital admissions, unplanned emergency room visits, and unplanned use of intravenous [IV] fluids).
Aim 3: Determine if CG self-efficacy mediates the effect of the intervention on CG anxiety.
Aim 4: Determine if patient illness factors, care demands (hours per week spent caregiving), and patient and CG demographic factors moderate the relationship between the intervention and CG outcomes.

Aim 4a: Examine which social determinants of health (aspects of vulnerability) in caregivers moderate the efficacy of the intervention.

Aim 4b: Explore caregivers' perspectives and experiences regarding the intervention to understand how the intervention should be modified to better serve vulnerable caregivers.
Aim 5: Compare the costs of healthcare utilization (unplanned hospital admission, unplanned emergency room visits, and unplanned use of IV fluids) between the intervention and control groups.

3.0 RESEARCH SUBJECT SELECTION AND ELIGIBILITY

Setting

Radiation Therapy Departments of the Seidman Cancer Center at the University Hospitals main campus, satellite community facilities, and MetroHealth Cancer Center.

Population

The sample will consist of family CGs of individuals with HNC, NSCLC, rectal, anal, and esophageal cancer. In this study, a family CG is defined as an adult who is providing daily assistance and/or emotional support to the individual with cancer as identified by the patient. The sample will be drawn from the population of patients at the Cancer Center. Data obtained from the Cancer Center tumor registry show that 403 adult patients with new diagnoses of HNC, rectal, anal, and esophageal cancer (all stages) and stage III NSCLC cancer were evaluated in 2017. Demographic characteristics were: 62.5% male, 37.5% female, 82.4% White, 16.4% Black, and a mean age of 64 years. Fifty-seven percent underwent radiation therapy.
The extension period will include family CGs and patients recruited from MetroHealth, an academic medical center and Cuyahoga County's safety-net health system. It is located in the City of Cleveland, which is racially and ethnically diverse (49% Black, 40% White, 11.9% Hispanic).

Sampling Procedure and Group Assignment

A convenience sample of family CGs will be used.

Inclusion criteria for patients are: (1) 18 years of age or older. (2) Diagnosis of stage I, II, III

cancers of the rectum and anus, stage I, II, III, IVa esophagus; stage II-III NSCLC (excluding those receiving SBRT due to short treatment course); and stage I – IV A/B head/neck (tongue, gum, oral cavity, nasopharynx, oropharynx, hypopharynx, parotid, or larynx). Stage IV A/B will be allowed for HNC and stage IVa for esophagus as the intent of therapy is curative. (3) Has an identified family CG who is willing to participate.

Inclusion criteria for CGs are: (1) 18 years of age or older; (2) family member or friend of an adult patient described above; and (3) identified by the patient as his/her primary CG, who is providing daily assistance and/or emotional support.

Exclusion criteria are: Patients who do not have a caregiver will be excluded. CGs of patients who are receiving hospice care will be excluded because of the patient's poor prognosis and multiple issues associated with end-of-life care. CGs who are themselves undergoing active cancer treatment will be excluded (hormonal treatment allowed).

Projected Enrollment

We estimate, based on the annual Cancer Registry data, that 131 patients with stage I, II, III rectal, anal, and esophageal cancers; stage III NSCLC; and stage I-IV A/B HNC will be receiving radiation therapy at the three study sites of the Cancer Center. Approximately 10% of these patients will not meet our eligibility criteria (e.g., no family CG), resulting in 118 potential participants annually. Based upon our current pilot study, *Building Family CG Skills Using a Simulation-Based Intervention for Care of Patients with Head and Neck Cancer,* we expect a CG refusal rate of 40%. Therefore, we project to enroll 71 CGs per year or 5 per month. We plan to enroll subjects for 36 months, resulting in an enrollment of 180 subjects over the course of the study. We will allow for a 10% dropout rate, resulting in 162 subjects for the final analysis. The estimated 10% attrition rate is based on a current caregiver intervention study in the Cancer Center, in which the rate is 9.7% (NR015464, Douglas PI).

While 40% is a high refusal rate, it is consistent with other intervention studies that aimed to enroll patient-caregiver dyads.[2,3,90] In addition, the use of incentives has been found to reduce the refusal rate in this CG population, and thus, we will offer a $100 incentive to all CGs for participation in the study. We will also seek IRB approval to collect additional information from CGs who refuse, including whether the CG is working and/or providing care to other individuals, which were common reasons for refusal in the pilot study. Lastly, we will monitor the refusal rate monthly. If the refusal rate is greater than 40% for more than 4 months, we will consider revising our strategies and seek other sites. We will offer a $40 incentive to all patients for participation in the study.

For the extension period, with the increased number of study sites we project to enroll 6 caregivers per month. We plan to enroll subjects for an additional 16 months, resulting in 96 subjects over the course of the extension project. We project that the parent study will enroll a total of 148 subjects. Adding the 96 subjects in the extension project will result in a total sample size between the parent study and extension project of 244. With an estimated dropout rate of 12%, the sample for the final analysis will be 214 dyads.

4.0 RESEARCH SUBJECT ENTRY

A convenience sample of family CGs will be used. Potential patients who meet the study inclusion criteria will be identified by the research assistant (RA) through review of the weekly radiation clinic schedules. The diagnosis will be confirmed in the medical record. Based upon pilot work, we have determined the optimal time to approach subjects for inclusion into the study is during the radiation therapy simulation visit, which is approximately 10 days prior to the start of treatment. Consent will be obtained in person.

The patient will be approached by the RA in a private room in the clinic and the study will be explained. The patient will be asked to identify an adult family member or friend who is his/her primary caregiver. We will ask for the patient's approval to talk with the caregiver about the study. *If the caregiver is present in the clinic,* the study will be explained with an opportunity for the caregiver to ask questions. Written consent will be sought from the patient and caregiver. *If the caregiver is not present at that time*, contact information for the caregiver will be obtained and the patient will be asked to give his/her caregiver an information pamphlet about the study. The RA will contact the caregiver within four days to explain the study and to set up an in-person meeting with the caregiver at the clinic. At that

meeting, written consent will be sought from the patient and caregiver.

For the duration of the COVID-19 pandemic, patient and caregiver consent will be obtained remotely by phone or electronically through Redcap whenever possible. If remote consent is not feasible due to the timing of treatment, patient or caregiver factors, or enrollment issues, we will return to our previous in-person consenting protocol, following all hospital guidelines regarding masking and distancing. The remote consenting protocol is as follows: at the new patient visit (NPV) or CT Simulation visit the radiation oncology staff, such as the Nurse Partner, will give the patient our IRB-approved study brochure and two (2) paper copies of the patient and caregiver consent forms. If the NPV is completed via telehealth or there are insufficient clinical notes to assess eligibility, the brochure and consent form will be given to the patient at the in-person CT simulation visit. The brochure contains opt-out information for patients who do not wish to be contacted about the study. Instructions are to call the study office telephone number to opt out of the study. This opt-out is a short time frame of 2 days, and will be pointed out to the patient by the medical staff. If no call or email from the patient is received within 2 days, the study team will call the patient and discuss the research using a script (attached). If the patient gives verbal consent to participate and identifies a caregiver, and the caregiver lives with the patient and is available, we will offer to speak with them together on the phone to answer any questions about the consent.

Secure REDCap links to the patient and caregiver consent forms will be sent to their preferred email addresses. The informed consent process will continue on the telephone and, after questions are answered, the patient and caregiver will electronically sign and date the REDCap consent forms. The consenter will also electronically sign and date the REDCap consent form. The enrollment procedure proceeds with contact information being completed via telephone.

If the patient and/or caregiver do NOT have email or internet access, informed consent will proceed via telephone with the patient and/or caregiver signing paper copies of the consent forms, previously provided by the medical staff. The patient and caregiver will mail the signed forms back to the researcher's office via a study-provided postage-paid envelope (also given at their health care provider visit) and will keep the unsigned copies. The enrollment procedure proceeds with contact information being completed via telephone.

Subjects' capacity to consent will be evaluated by the RA in conjunction with the clinical team. Participants must be cognitively intact, as evidenced by orientation to person, place, and time. They must be able to speak, read, and comprehend English.

All participants are volunteers and non-participation and withdrawal from the study are alternatives to study participation. Patients and caregivers will be told that they may withdraw from the study at any time. There are no risks to non-participation or withdrawal from the study. The RA will explain that participation or non-participation will have no effect on the care that the patient and caregiver will receive from the healthcare team.

For the extension period, caregivers will be offered an additional qualitative interview after completing the intervention. The consent form will give caregivers a choice to opt in and agree to be contacted for an interview. Caregivers randomized to the intervention will be selected for interviews using purposive sampling to select participants with a low score in at least one domain of the social determinants of health. Interviews will be done with 15 caregivers who opted in during the consent process. The interviews will take place after they have completed the intervention.

Once consent is obtained, baseline measures will be collected. All participants will be screened for health literacy using a 4-item Brief Health Literacy Screening Tool (BRIEF), a self-report tool that assesses comprehension to written and verbal health information as well as confidence in filling out medical forms. The research team will employ communication and teaching strategies from AHRQ's Health Literacy Universal Precautions Toolkit[94] for individuals identified as having limited health literacy.

Once baseline data have been obtained, the Project Director will randomly assign the CG to one of

two groups: control or intervention. Randomization will be done using the minimization stratified randomization technique (QMinim). Minimization is designed to balance pre-identified stratifying covariates across treatment assignments more effectively than simple randomization.[87-89] Stratification variables will be CG gender, CG age, and patient cancer type.
The RAs will be blinded to group assignment.

We will not request a waiver for consent documentation from the IRB. We will request partial waiver of HIPAA Authorization due to the need to review the radiation oncology patient schedule to determine potential participants. We will use the following identifiable information in screening for participants in the study: patient name, diagnosis, medical record number, date and time of appointment, and family caregiver name and contact information. The identifiable information will be used only by members of the research team and will be stored on RedCap and UH Box. Identifiers of non-participants will be destroyed when the study is closed to enrollment.

5.0 STUDY DESIGN AND METHODS

5.1 Design/Study Type

This is a 2-group, prospective, randomized controlled design to test the effect of an intervention, as compared to a usual care control group, on CG outcomes, patient outcomes, and healthcare utilization outcomes during treatment. As shown in Table 2, the intervention involves three in-person, one-on-one teaching sessions with the caregiver during radiation treatments, followed by a telephone booster contact 2 weeks posttreatment. We will collect patient and CG data at baseline (T1), at the end of radiation treatment (T2), and 4 (T3), and 20 weeks (T4) postradiation treatment. We opted to measure outcomes at the completion of radiation treatment (and midintervention) because we want to compare groups when side effects, which develop gradually during radiation therapy, are intense. The timing of measures after treatment was based on our longitudinal descriptive study of patients with HNC and our clinical experience of the trajectory of patient recovery after treatment. The total number of weeks of radiation treatment may vary depending on the specific diagnosis. Therefore, measures taken at T3 and T4 are based on time since completion of radiation treatment. The independent variable is group assignment.

Table 2. Design Schematic

	Treatment Phase			*Posttreatment Survivorship Phase*		
	T1 1st week XRT	3rd week XRT	***T2*** End XRT 6th – 8th week	2 weeks post XRT	***T3*** 4 weeks post XRT	***T4*** 20 weeks post XRT
Intervention	X	X	X	X_T		
Data	M		M		M	M

Note. XRT = Radiation treatment; X = In-person intervention; X_T = Intervention booster telephone call; M = Measurement.

The primary outcome is CG anxiety. Secondary outcomes are CG depression, HRQOL, and fatigue; patient HRQOL and interrupted treatment; and healthcare utilization outcomes. The mediating effect of self-efficacy will be assessed as well as the moderating effects of patient illness factors, care demands, and demographic factors.

The study design during the extension period will not change, except for the addition of a qualitative interview. We will conduct qualitative interviews with a subset of 15 caregivers exploring their perspectives and experiences regarding the intervention.

5.2 Selection of Instruments

We chose measures based on our prior work with caregivers that are psychometrically sound and/or recommended by NIH as common data elements to facilitate cross-study analysis and increase the scientific impact of our study analyses. The instruments can be found in Appendix A.

Caregiver Outcome Variables

The Patient-Reported Outcomes Measurement Information System (PROMIS) will be used to measure caregiver outcome variables. The PROMIS item banks and their short forms were developed and calibrated using item-response theory on large data samples from patients with chronic conditions (including cancer) and the US general population. Reliability and precision of the items in measuring various constructs have been reported by Cella et al.[95] For each survey, the responses are summed to produce a total raw score, which is converted to a T-score. Higher T-scores represent greater amounts of the construct being measured. Each survey, in our experience, takes approximately two minutes to complete.

Anxiety will be measured with the PROMIS Anxiety Short Form 7a.[95] This 7-item questionnaire assesses self-reported fear, worry, anxiety, tension, nervousness, and restlessness in the family caregiver over the last 7 days.

Depression will be measured with the PROMIS Depression Short Form 8b.[95] This 8-item questionnaire assesses caregiver self-reported negative mood (sadness, guilt), views of self (worthlessness), and social cognition (loneliness), as well as decreased positive affect and engagement. It assesses depression over the last 7 days.

HRQOL will be measured using the PROMIS Global Health Scale v.1.0/1.1, a 10-item questionnaire that evaluates global physical health and global mental health.[95] Caregiver fatigue will be measured with the PROMIS Fatigue Short Form 7a, a 7-item questionnaire that evaluates the self-reported experience of fatigue (frequency, duration, intensity) and the impact of fatigue on daily activities.[95] It assesses fatigue over the last 7 days.

Caregiver Reaction Assessment will be used at baseline and at time 3 (4 weeks post-XRT) to measure caregiver's reactions to caregiving for family members with an illness. The scale uses a Likert response format.

Patient Outcome Variables

HRQOL in patients will be measured using the disease-specific versions of the FACT-G that include common HRQOL subscales (physical, social, emotional, and functional well-being) plus cancer-specific questions. We will analyze the effect of the intervention on HRQOL across diagnoses using the common FACT subscales and will describe the symptom experience within each diagnostic group using the cancer-specific FACT subscale. Respondent burden is minimal with the FACT surveys, with a completion time on average of 5 to 10 minutes.[114] Participants rate their response to each item on a 5-point Likert-type scale. After reverse-scoring negatively worded questions, items are summed. Higher scores indicate better quality of life. Reliability and validity of the FACT-G scale was established in a sample of 854 patients with cancer.[115]

The Functional Assessment of Cancer Therapy - Colorectal (FACT-C, Version 4) is a 37-item questionnaire that measures self-reported HRQOL in patients with colorectal cancer over the last 7 days.[96] Good internal consistency, concurrent validity, and sensitivity to change over time were supported.[96]

The Functional Assessment of Cancer Therapy - Head and Neck Scale (FACT-H&N, Version 4) is a 39-item questionnaire that assesses self-reported HRQOL in patients with head and neck cancer over the last 7 days.[98] Good internal consistency of the FACT-H&N was reported for the total scale (alpha = 0.89).[98] Convergent versus divergent validity was demonstrated when compared to the Performance Status Scale for Head and Neck Cancer Patients (PSS-HN) in a sample of patients with head and neck cancer receiving various cancer treatments.[98]

The Functional Assessment of Cancer Therapy - Esophageal (FACT-E, Version 4) is a 44-item questionnaire that measures self-reported HRQOL in patients with esophageal cancer over the last 7 days.[97] Excellent internal consistency of the FACT-E subscales was reported (alphas > 0.70).[98] Convergent versus divergent validity was demonstrated when compared to the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ) and esophageal (OES 24) in a sample of patients with esophageal cancer treated with surgery with or without

chemoradiation.[98]

The Functional Assessment of Cancer Therapy - Lung (FACT-L, Version 4) is a 33-item questionnaire that measures self-reported HRQOL in patients with lung cancer over the last 7 days.[104,105] Psychometric properties of the FACT-L were assessed by Cella et al.[104] in a sample of 116 patients with various types and stages of lung cancer. Internal consistency, construct validity, and sensitivity to change was established.

Interrupted Radiation Treatment Course, defined as the total number of missed treatment days due to patient or caregiver reasons, will be determined from the patient's radiation therapy treatment record. We will also record the duration (number of days) of each episode of absence from treatment.

Healthcare Utilization Outcomes

Healthcare utilization outcomes include unplanned hospital admission, unplanned emergency room visits, and unplanned IV fluid use for treatment of dehydration. We will evaluate the effects of the intervention, as compared to the control group, on these outcomes, as well as describe the costs associated with these outcomes. These outcomes will be measures at T2, T3, and T4.

Mediating Variable

Caregiver self-efficacy for caregiving will be measure with the Caregiver Inventory, a 21-item questionnaire that evaluates the domains of managing medical information, caring for the care recipient, caring for oneself, and managing difficult interactions and emotions.[99] This scale will be administered at all time points. Participants rate each item on a nine-point scale, ranging from *not at all confident* (1) to *totally confident* (9). Scores are summed, with higher scores indicating greater confidence. Psychometric properties of the Caregiver Inventory were initially reported on data from 133 family caregivers of terminally ill patients.[99] The Cronbach alpha was 0.91 and validity was supported through correlational analyses with other measures (Perceived Stress Scale and Caregiver Burden Inventory) as well as ratings by caregivers and social workers of caregiving tasks.[99]

In addition, an investigator-constructed survey to measure self-efficacy for specific caregiving skills during radiation therapy will be used for descriptive purposes. Caregivers will rate their confidence in performing specific skills on a 10-point scale.

Covariates

Patient illness factors – stage of cancer, time since diagnosis, treatment type (chemoradiotherapy vs. radiotherapy alone), HPV status (in HNC and anal cancer), use of palliative care, and patient performance status – will be recorded on the enrollment form. Updates for use of palliative care and patient performance status will be noted at T2, T3, and T4. Care demands, defined as hours/week spent caregiving, will be assessed at all time points. Demographic characteristics of both the patient and caregiver will be collected at baseline (T1). Use of mental health interventions (support group participation, social work and/or psychologist Involvement) will be assessed at all time points.

Three additional measures of social determinants of health are health insurance, social support, and financial toxicity. Health insurance will be assessed at baseline for patients and caregivers. Patient health insurance status will be obtained in the medical record, and caregiver insurance status will be obtained through self-report. Financial toxicity will be assessed with the Comprehensive Score for Financial Toxicity measure (COST), a patient-reported outcome measure that includes an 11-item scale and a single summary item of financial hardship. All items are rated on a 5-point Likert scale and lower scores indicate greater financial toxicity. The COST measure has been found to be reliable and valid in assessing caregiver financial toxicity. The 19-item Medical Outcomes Study (MOS) Social Support Survey will be used to measure perceived social support. The survey provides an overall support index score, as well as domain scores for emotional/informational, tangible, positive interaction, and affectionate support. Higher scores indicate greater support. The Ohio Opportunity Index (OOI), which measures health and well-being based on home address,

will be used to describe neighborhood characteristics for caregivers.

Other variables

Intervention dose, defined as the number of intervention sessions the caregiver receives, will be recorded at the completion of the intervention.

Other variables associated with cost analysis

Nurse time for preparation of the simulation and delivery of the intervention (in-person and phone contacts) will be collected prospectively during the study period. CGs will be surveyed at each intervention contact (during radiation weeks 1 and 3, and at the end of radiation treatment) regarding any travel expenses for meetings with the intervention nurse.

5.3 Description of Intervention

The intervention was designed over a one-year period in collaboration with a small team of oncology clinicians. Our focus was to design an intervention that would address the specific, complex challenges of family CGs, while maintaining feasibility for implementation into a busy clinic schedule. The intervention is delivered by an experienced oncology nurse, trained in intervention components, during the patient's course of radiation treatments. It consists of three in-person sessions between the CG and intervention nurse (interventionist) and one follow-up telephone contact after treatment is completed (Table 3). The intervention design was validated by:

- Review of CG intervention literature (primary and meta-analytic research)
- Use of an explicit conceptual framework
- Expert opinion from oncology clinicians
- Our prior descriptive studies
- Qualitative interviews with participants in the pilot study regarding satisfaction and acceptability

Decisions regarding timing and duration of the intervention were based on clinical experience and our longitudinal, descriptive study of patients with HNC, which clearly illustrated the pattern of increasing intensity of side effects through the weeks of radiation treatment and one-month posttreatment. In addition, a systematic review of cancer CG interventions found that problem-solving and skill-building interventions were effective in increasing CG confidence if the interventions were structured, of brief duration, and targeted to specific caregiving needs along the care trajectory.[91] Therefore, based on our clinical experience and these findings, we designed three CG sessions and one telephone follow-up to coincide with the typical patient's experience. **Each session lasts approximately 30 minutes.** The nurse interventionist will record the amount of time required for preparation and delivery of each session. For the duration of the COVID-19 pandemic, sessions 2 and 3 will be delivered by phone rather than in-person. The first session will remain in-person in the radiation oncology clinic or the CWRU School of Nursing if caregivers are not allowed in the hospital. All simulation requiring the mannequins will be completed at that first in-person session. We will also offer an in-person option for sessions 2 and 3 if the caregiver requests additional skills training with the manikins.

The themes of the intervention session are: (1) the patient's experience, (2) the CG experience and the patient-CG relationship, and (3) the transition to posttreatment survivorship. Each session is standardized in that it begins with addressing any issues or concerns that the CG may be experiencing, assessing the CG's level of distress, and providing emotional support. This is followed by provision of relevant information related to the theme of the session, followed by the simulation experience.

Five simulation protocols with corresponding scenarios were developed by the PI in collaboration with the team of oncology clinicians. The **technical simulations training** with a tracheostomy tube, gastrostomy tube, and skin and ostomy/wound care use a low-fidelity manikin. The **communication skills**

training use common caregiving scenarios to stimulate discussion, identify barriers, and solve problems. Communication skills include asking questions, active listening, staying calm, expressing feelings, recognizing depressive feelings, and identifying resources for both the patient and CG. The **self-care simulations** include specific skills for CG self-care, including identifying strategies to reduce fatigue and improve sleep, prioritizing activities, taking time for leisure activities, finding support, and managing one's own health care. Two radiation oncology nurses, a surgical nurse, and a psychiatric clinical nurse specialist reviewed each simulation protocol for content validity and consistency with nursing practice guidelines.

The simulation protocols were modeled after procedures used in nurse education. They contain: (1) CG learning objectives; (2) presimulation preparation, during which the intervention nurse shows the CG the manikin and reviews steps of the procedure; (3) simulation scenarios that are basic and more complex (alternative scenarios) and have a series of critical events that the CG responds to; and (4) a postsimulation debriefing during which the intervention nurse answers questions, assesses the CG's confidence in performing the skills, and provides additional training as necessary. Each simulation manual includes a structured checklist with scenarios, expected CG behaviors, and nurse prompts. Although the simulation training will follow a consistent outline, the content will be tailored to the CG's needs. CGs will have the opportunity to repeat simulations at each session. CGs will be offered a flashlight by the interventionist if they do not have one at home to use for oral assessments. An example of a simulation checklist is shown in Figure 2.

Table 3. Intervention Components

	Session One	Session Two	Session Three
Time	**First 10 days of XRT**	**3rd – 4th week of XRT**	**Completion of XRT**
Goal of session	Help CG understand the PT's experience and how to help	Review strategies for current care issues PLUS describe the typical CG experience and how the disease may affect relationship between CG and PT	Review strategies for current issues PLUS discuss common issues and concerns that may arise after cancer treatment
Content			
1. Support (Normalize concerns or experiences, listen, assess & respond to distress)	Assure CG that healthcare team will assist him/her in managing issues. -Assess CG distress & refer to SW if score ≥ 5/10 -Identify resources & sources of social support for CG	-Discuss current PT issues or symptoms. -Ask, "What would you like to review today?" -Assess CG distress & refer to SW if score ≥ 5/10 -Identify resources and sources of social support for CG	-Discuss current PT issues or symptoms. -Ask, "What would you like to review today?" -Assess CG distress & refer to SW if score ≥ 5/10 -Identify resources and sources of social support for CG
2. Information (Using intervention manual and NCI booklet, provide specific information related to session theme)	-Describe what the PT will face during treatment. -Review treatment fields using anatomical model -Provide information about 5 most common PT side effects & strategies for management (these vary by diagnosis) -Provide information about fatigue, mood, and anxiety, pain, & skin care	-Describe the typical CG experience and discuss CG self-care. Provide information about common CG concerns and strategies for self-management: Emotional concerns (distress, anxiety, worry, depressive symptoms) Physical concerns (sleep problems, fatigue, changes in appetite or weight) -Describe common issues that may arise in the relationship -Provide information about 5 most common concerns and strategies for coping: Shifting or changing roles, communication difficulties, new feelings or emotions that may be expressed, changes and disruptions in lifestyle (restricted living), and changes in intimacy	-Describe common issues that may arise in the posttreatment transition -Provide information about common concerns and issues during immediate transition to posttreatment survivorship: PT physical issues, PT and CG emotional responses, financial and work issues, CG ability to provide ongoing care, advance care planning, urgent issues & when to call the healthcare team
3. Simulation (Practice skills & complete scenarios)	Practice technical skills & receive feedback from interventionist regarding competency: PEG tube feeding, tracheostomy tube care and suctioning, ostomy care, skin care	Repeat technical skills simulation (per CG request or if interventionist deems necessary to improve competency) Communication skills: Use scenarios to practice asking questions, active listening, staying calm, expressing feelings, and recognizing depressive feelings Self-care skills: Use scenarios to discuss strategies to reduce fatigue, improve sleep, and promote CG health.	Repeat skin care skill training with attention to posttreatment skin changes & issues Repeat other skills simulations (per CG request or if interventionist deems necessary to improve competency)

Note. XRT = Radiation therapy; CG = Caregiver; PT = Patient; SW = Social Worker.

Evaluation of each session, including CG competency during simulations, will be done by the intervention nurse (Figure 3). During the simulations, CG performance of expected behaviors will be assessed and noted by the intervention nurse on the simulation checklist. The CG level of skill acquisition will be determined by the percent of behaviors completed correctly and will be noted as little/none (less than 30% behaviors performed), some (30% - 75%), or great (more than 75%). Following the three in-person sessions, the intervention nurse will make a telephone contact two weeks after treatment to address any transition issues, to discuss any persistent side effects or issues, and to review self-care strategies for the CG.

The **intervention "dose"** is defined as the number of sessions that the participant receives. The optimal intervention dose for cancer CG interventions is unknown. In a meta-analysis of CG interventions by Northouse et al.,[2] the number of intervention sessions ranged from 2-12 and the duration of interventions ranged from several days to 18 months. Based on our pilot work, we tapered the dose of the intervention to three in-person sessions and one telephone session. We hypothesize that an adequate intervention dose is 3 of the 4 sessions and we will analyze the effect of intervention dose on the outcomes.

Figure 2. Simulation – PEG Tube Feeding

Caregiver Learning Objectives: (1) Describe equipment needed. (2) Describe steps in process of giving a tube feeding. (3) Demonstrate tube feeding. (4) Communicate observations that are necessary for safe feeding.

Pre-Simulation Preparation				
	Intervention Component		**Done (yes/no)**	**Notes**
1	Explain purpose of simulation – to learn the skill of tube feeding			
2	Show CG manikin and encourage CG to touch manikin			
3	Review needed equipment and emphasize need to maintain clean technique			
4	Review and give CG a copy of UH booklet, *Your Peg Tube Guide*			
5	Assess for CG questions and provide answers			
Simulation Scenario				
	Manikin Actions	**CG Expected Behaviors**	**RN Cue Ask about…**	**Behavior Yes/No**
1	Manikin is supine	Gathers necessary clean equipment	method (bag vs syringe)	
		Checks date on formula		
		Helps patient to sitting position or 45 degrees		
		Washes hands		
		Pours the ordered amount of formula into the feeding bag	temperature of feeding	
		Hangs bag on pole or hook at required height		
		Allows tubing to fill with formula		
		If instructed by doctor, checks for stomach contents using a syringe. If there is less than the recommended amount, pushes it back in and proceeds with feeding.	***Review Page 21-23 of booklet	
		Using a syringe, flushes tube with prescribed amount of tap water before feeding.	amount and temp. of water	
		Connects PEG tube to feeding bag		
		Opens clamps to begin feeding	duration & speed	
		Using a syringe, flushes tube with prescribed amount of tap water after feeding		
		Reclamps tube when water is in Disconnects tube feeding and reapplies cap		
		Assists patient to remain sitting or at 45 degrees for 30 min.	care of equipment	
Alternative Scenarios				
2	Leakage around tube	Verbalizes that he/she would stop the feeding and call the doctor right away		
3	Tube pulls out or comes out part-way	Verbalizes that he/she would call physician right away or visit emergency department for replacement of tube Verbalizes that the tube should not be used		
Post-Simulation Debriefing				
	Intervention Component		**Done (yes/no)**	**Notes**
1	How did you feel performing as the CG in this experience?			
2	What part of the experience went well? What steps are you confident performing?			
3	What steps do you need more practice with?			
4	What further questions do you have?			

5.4 Data Collection

For patients and caregivers in both the intervention and control groups, study measures will be obtained in-person, via mail, via an emailed RECap survey or by telephone by the RA at baseline (T1), at the end of treatment (T2), and at 4 (T3) and 20 (T4) weeks posttreatment. RAs will ask for permission to use text reminders if participants agree to receive texts. Instruments can be completed in 10 minutes (Table 4). Surveys will be self-administered, but can also be administered by interview format if needed. We chose measures based on our prior work with caregivers that are psychometrically sound and/or recommended by NIH as common data elements to facilitate cross-study analysis and increase the scientific impact of our study analyses.

Data will be collected primarily using Research Electronic Data Capture (REDCap). However, there will be times when we will be unable to meet with the participant and paper data forms will be

necessary. All subject data (patient and caregiver) will be entered into a database using an assigned code number. No names or identifying variables will be with the actual data. The database will be kept on a password-protected database in REDCap (described below) and SPSS and downloaded to an encrypted computer drive.

All subject data will be initially stored on the UH application of the REDCap database. It stores data in the UH Data center, encrypted using SSL encryption. Access to the data requires a username and password combination, authorized by the system administrator. The study log, linking subjects' identifiers with their code number, will also be stored on REDCap. The de-identified data from REDCap will be downloaded to a password-protected encrypted drive that will be kept in a locked office in the School of Nursing, as described above, when ready for data analysis. The separate passwords for the data files will only be known to the PI, project manager, research assistants, and nurse interventionists.

Consent forms, the only paper form containing names, and any paper data forms will be kept separately in locked file drawers, in a locked study office in the School of Nursing.

The weekly schedules, enrollment log, and tracking log will be stored on a study-specific UH Box site because they are dynamic Excel files that are used daily by the CWRU research team.

During the extension period, qualitative interviews will be conducted either in-person, by phone, or using UH Zoom based on caregiver preference. The interviewer will follow the interview guide, adding prompts and follow-up questions as appropriate. Interviews will last approximately 30 to 45 minutes. Interviews will be recorded and the data file will be uploaded to UH Box for storage.

Table 4. Study Measures

VARIABLE	INSTRUMENTS	TIME T1	T2	T3	T4
CG Outcomes					
CG Anxiety	Patient Reported Outcomes Measurement Information System (PROMIS)[95] Anxiety Short Form 7a	X	X	X	X
CG Depression	PROMIS[95] Depression Short Form 8b	X	X	X	X
CG HRQOL	PROMIS[95] Global Health Scale v.1.0/1.1	X	X	X	X
CG Fatigue	PROMIS[95] Fatigue Short Form 7a	X	X	X	X
Patient Outcomes					
HRQOL	FACT-C, v. 4, [96] FACT-E, v. 4,[97] FACT-H&N, v. 4,[98] and FACT-L, v. 4[104, 105]	X	X	X	X
Interrupted radiation treatment course (total number of missed days from treatments)	Radiation Therapy PT treatment record		X		
Healthcare Utilization Outcomes					
Unplanned hospital admission	Hospital record		X	X	X
Unplanned emergency room visits	Hospital record		X	X	X
Unplanned intravenous fluid use	Hospital record (number of liter bags used)		X	X	X
Cognitive Mediator					
CG self-efficacy for caregiving	CG Inventory[99]	X	X	X	X
	Investigator-constructed self-efficacy scale for managing side effects & specific skills	X	X	X	X
Potential Moderators (Covariates)					
Patient Illness Factors (Stage; time since diagnosis; treatment type, e.g., concurrent chemotherapy; HPV status in HNC and anal cancer)	PT medical record	X			
Use of palliative care services	PT medical record	X	X	X	X
PT Performance Status	ECOG Performance Status[100,101] (patient)	X	X	X	X
Care Demands (hours/week spent caregiving)	Interview questions (CG)	X	X	X	X
Demographic characteristics (race, marital status, employment status, health insurance, socioeconomic status)	Interview questions (CG and PT)	X			
Use of mental health interventions (support group participation, social work and/or psychologist involvement)	Interview questions (CG and PT)	X	X	X	X
Financial toxicity	COST-FACIT (version 2)		X		X
Social support	MOS		X		

Note. PT = Patient; CG = Caregiver; ECOG = Eastern Cooperative Oncology Group; ADLs = Activities of daily living. CG age, CG gender, and PT cancer type will be used in the minimization stratified randomization technique. Number/types of care demands will be collected as descriptive data.

5.5 Description of Study Process

5.51 Instrument Administration

Prior to data collection, both RAs and the Project Director will be trained by the PI in the administration of the data collection tools. For patients and caregivers in both the intervention and control groups, study measures will be obtained in-person, via mail, via Redcap survey, or by telephone by the RA.

5.52 Intervention Administration

Caregivers in the intervention arm will receive individual support, education, and training that incorporates simulation techniques focused on skill development and communication. The intervention will occur during three in-person sessions between the caregiver and intervention nurse (interventionist) during the patient's course of radiation therapy. The intervention will be delivered in a private room in the Radiation Therapy Department. The themes of the intervention session are: (1) the patient's experience, (2) the caregiver experience and the patient-caregiver relationship, and (3) the transition to posttreatment survivorship. One follow-up telephone contact will occur after treatment is completed.

Caregivers randomized to the control group will receive per usual care, the NCI booklet, *When Someone You Love is Being Treated for Cancer.*

Caregivers in both groups will receive usual care by nonstudy clinicians, which includes a weekly visit with the radiation oncologist and clinic nurse for the patient and CG. The weekly visit is brief (10-15 minutes) and focused on how the patient is tolerating the radiation treatments and management of any treatment side effects.

5.53 Special Concerns

Retention of caregivers. Various retention strategies will be employed. Retention will be maximized by: (a) consistent contact with the same intervention nurse, (b) minimizing amount of time needed to complete surveys, (c) delivering the intervention during scheduled radiation treatment visits, (d) conducting the intervention booster telephone call at a time convenient for the subject, and (e) mailing a reminder letter midway between T3 and T4 surveys to keep patients and caregivers engaged during the long gap in study contact.

5.54 Compensation

To compensate for time spent and to reduce attrition, caregiver participants will receive a $50 gift card after completing measures at 4 and 20 weeks post-treatment (T3 and T4), for a total of $100. Patient participants will receive a $20 gift card after completing measures at 4 and 20 weeks post-treatment (T3 and T4) for a total of $40.

During the extension period, caregivers who participate in the qualitative interview will receive an additional $30 gift card.

5.6 Adverse Reactions and Their Management

5.61 Reporting Adverse Events

Data and Safety Monitoring Plan

a) Monitoring Entity
   A Safety Monitoring Committee (SMC) will be formed for this grant. The SMC will consist of members outside the study team, including two faculty members from the Frances Payne Bolton School of Nursing, CWRU and a physician from the Case Comprehensive Cancer Center. Study team members will include: Dr Susan Mazanec, PI, and Dr. Nicholas Schiltz, Statistician. The chair of the committee (an outside member to be named) will be responsible for submitting reports to NCI within 2 weeks of the meeting. The committee members who are outside the study team will review data on the study as provided by Drs. Mazanec and Schiltz and will conduct random auditing of the research records to assess study safety and regulatory compliance.

b) Data Safety Monitoring Committee
   Twice annually, throughout the project, this committee will review data on this study regarding: (1) study safety including auditing selected cases for compliance with IRB requirements, (2) conformance with informed consent requirements, verification of source documents, and

investigator compliance, (3) minimizing research-associated risk, and (4) protecting the confidentiality of participant data. In addition, it will review all causes of mortality and issues with participation. The rate of recruitment refusal (percent and reasons) and subject attrition (percent and reasons) will be tracked and reported at these reviews. Differential attrition from all study groups will be monitored. If concerns or problems are identified by the SMC, they will be reported to the IRB and NCI/NIH via email by the SMC within 3 business days after they are identified. If there are recommendations made by the SMC, the action plan for response or notice of any actions taken by the IRB regarding the research and any responses to those actions will be provided to NCI officials within 2 weeks.

c) Adverse and Unanticipated Events

At the onset and across the duration of the study, all staff and investigators will have instructional review of the nature and types of unanticipated and adverse events as described by NCI and the University Hospitals IRB. As they occur, all unanticipated events and adverse events will immediately be reported to the principal investigator who will report them to the IRB according to the IRB protocol for both serious and non-serious adverse event and unanticipated problem reporting. These will be summarized in reports to the SMC twice a year. Annual progress reports to the IRB and NCI/NIH will include a summary of the SMC's activities and findings as well as any adverse events regarding human subjects. Program officials at NCI will be informed within 3 business days of unanticipated problems (e.g. data breach) or unexpected serious adverse events that may be related to the study protocol or IRB-approved revisions to the study protocol that indicate a change in risk for participants.

Although this study is deemed as having minimal risk, we recognize that some unanticipated or adverse events could occur. These situations will be noted and reported at the next SMC meeting.

Some subjects may have personal situations that may cause them to contact our project staff for assistance. If a subject contacts us requiring assistance of any kind, we will note that and give them United Way's "First Call for Help" telephone number and website information (www.211cleveland.org). They provide resources on various issues (legal, housing etc.) and can put the caregiver in touch with the appropriate organization in their hometown if necessary. If we obtain data that reveal concerns with patient care, the PI will share that information with the appropriate healthcare providers. If we obtain data that reveal concerns with mental health issues, we will put the caregiver in touch with a social worker, psychologist, or psychiatrist associated with the University Hospitals Seidman Cancer Center or MetroHealth Cancer Center. These situations will be documented and reported to the IRB and to the SMC and reviewed as necessary for protocol implications. For serious adverse events, the PI will report to the IRB within 3 business days, even if presumed to be unrelated to the study protocol.

5.62 Anticipated Reactions

Family caregivers will complete surveys about self-efficacy for caregiving, anxiety, depression, health-related quality of life, and fatigue. Patients will complete surveys about their HRQOL. There is a possible risk that the questions may evoke emotions in the subject, including anxiety, sadness, or regret.

There is a possible risk of a breach in confidentiality, including accidental disclosure of protected health information during the study or with data sharing. This research presents no more than minimal risk to the participants and involves no medical treatment. There are no alternative treatments or procedures.

5.63 Reaction Management & Protections against Risk

All research staff will receive training in human subjects research via the online Collaborative Institutional Training Initiative (CITI) and will undergo research credentialing procedures at University Cleveland Medical Center. In keeping with good clinical practice policy (NOT-OD-16-148), we will ensure that all key personnel and staff receive approved training in Good Clinical Practice Training. Documentation of successful completion of the training will be kept in our NIH Regulatory Binder.

The consent form will specifically address the risk that the surveys may evoke emotions. Subjects will be told the range of topics addressed in the surveys and will be informed that they can skip a question if they wish and/or stop the interview at any time. If during the data collection interview a subject becomes distressed, we will provide a referral (with the subject's permission) to the social worker for further assessment and support. The nurse interventionists will assess distress for the caregiver subject group and explore the nature of their distress. They will make a professional assessment as to whether the caregiver needs a professional referral. We are assessing caregiver depression and anxiety using the PROMIS measures. Since these two constructs are highly correlated, we will use the depression screening as a tool to determine whether the caregiver subject needs a referral. A score of 1.5 standard deviations above the general population will be considered the threshold to make a referral to the oncology social worker. The research assistant will be collecting these data and there is a calculated field in REDCap that will notify the research assistant if the caregiver subject has scored above the threshold.

For the duration of the COVID-19 pandemic, in-person contact with research staff will be limited to one session with the nurse interventionist for caregivers randomized to the intervention group. Nurses will follow UH and CWRU policies regarding symptom screening and masking for both the nurse interventionist and the caregiver. All equipment used in the intervention will be sanitized thoroughly before and after use. Intervention caregivers who screen positive for COVID-19 symptoms will not be eligible to participate in the study. They will be informed of their ineligible status and told to contact their PCP regarding testing and treatment. If a nurse interventionist screens positive, they will not meet with any subjects and will follow CWRU policies regarding return to work. Another interventionist will meet with the caregiver instead. If the interventionist tests positive for COVID-19, CWRU Employee Health and the UH IRB will be notified immediately and we will follow their guidance to make sure that research subjects who met with that interventionist recently are notified and given appropriate guidance.

As part of protection of human subjects, data will be protected as well. Access to the database will be limited to the project team. Data and the study log, linking subjects' identifiers with their code number, will be stored on REDCap. The de-identified data from REDCap will be downloaded to a password-protected encrypted drive that will be kept in a locked office in the School of Nursing, as described above, when ready for data analysis. The separate passwords for the data files will only be known to the PI, project manager, research assistants, and nurse interventionists. Consent forms, the only paper form containing names, and any paper data forms will be kept separately in locked file drawers, in a locked study office in the School of Nursing. Data sharing with other investigators will occur once human subject identifiers have been removed from the data set and a data-sharing agreement has been obtained.

6.0 STATISTICAL ANALYSIS

6.1 Primary and secondary endpoints.

The primary endpoint is difference in caregiver anxiety between the intervention and control groups at 20

weeks post-radiation treatment. Secondary endpoints are caregiver anxiety at the end of radiation treatment and 4 weeks post treatment; caregiver depression, HRQOL, and fatigue at the end of treatment and 4 weeks post-treatment; and patient HRQOL at the end of treatment and 4 weeks post-treatment.

6.2, 6.7, 6.8 Statistical Design, Power, Analysis plan, & Missing data.

An intent-to-treat analysis is planned. Before carrying out inferential statistical procedures, exploratory data analysis will be performed: all variable distributions will be examined and descriptive summery statistics will be provided: including means, standard deviations, and ranges for continuous variables, as well as percentages and frequencies for categorical variables, will be provided to describe the study sample. Variable transformations will be made in cases where distributions are skewed, or otherwise fail to meet the assumptions for analyses; nonparametric procedures will be used where transformations would be inappropriate. Plots will be used to describe the data and identify outliers and influential observations.

Aim 1

Analysis. The primary analysis for Aim 1 will be to compare the control and CG intervention arms with respect to CG anxiety at T4 (20 weeks postradiation treatment). A linear mixed model repeated measures analysis will be used to obtain mean changes from baseline in anxiety scores at Times T2, T3, and T4, using baseline anxiety as a covariate, also adjusting for covariates described in Table 4. A contrast of means will be constructed to compare arms with respect to change in anxiety at T4 (primary analysis) at the 0.05 significance level. In addition, the baseline characteristics of the two treatment groups will be compared using appropriate 2-sample tests for continuous or binary outcomes, and in a secondary analysis, characteristics found to differ between groups at baseline will be adjusted for in the linear mixed model. A secondary analysis will test for differences between groups at the other postbaseline time points, using the Tukey method to control the familywise error rate on a per outcome basis. Other CG outcomes will be compared between groups using a similar approach.

Power. With 180 subjects randomized and a 10% dropout rate, the sample size for the primary analysis will be 162 CGs (81 per arm). Assuming a correlation of 0.50 between CG anxiety scores at baseline and T4, when adjusting for baseline anxiety, a difference in means of 0.36 standard deviations (*SDs*) can be detected with 80% power using a 2-sided test with significance level 0.05, where *SD* is the within-group standard deviation of anxiety scores at Time T4. Here, adjustment for baseline anxiety reduces the detectable effect size from 0.41 to 0.36. This effect size (Cohen's d) is intermediate between a "small" (0.2) and "moderate" effect size, as defined by Cohen, [106] and is close to the pooled estimate of 0.29 from a meta-analysis of interventions (psychoeducational, skills training, and therapeutic counseling) with family CGs of cancer patients.[2] For other outcomes, there is 80% power to detect effect sizes of 0.41 *SDs* with a 2-sided test, significance level 0.05.

Aim 2

Analysis. This aim is to measure the effect of the intervention, as compared to a control group, on patient outcomes (HRQOL, interrupted treatment course) and healthcare utilization outcomes (unplanned hospital admissions, unplanned emergency room visits, and unplanned IV fluid use). Most outcomes will be count variables enumerating the cumulative numbers at T2, T3, and T4, which can be analyzed using Poisson regression methods implemented as generalized linear models, possibly allowing for overdispersion. Zero-inflated Poisson or negative binomial models[107,108] will be considered if the data indicate a higher frequency of zeros than predicted by a Poisson model. HRQOL, a continuous measure, will be analyzed using a linear mixed model with repeated measures at T1, T2, T3, and T4. We will analyze the effect of the intervention on HRQOL across diagnoses using the common FACT subscales and will describe the symptom experience within each diagnostic group using the cancer-specific FACT subscale.

Power. From our pilot study, in the control group we expect means of 0.29 and 0.25 for the number of unplanned missed days and number of unplanned hospital admissions, respectively. In a Poisson regression model, sample sizes of 81 patients per group will provide 80% power to detect a 68% reduction in unplanned missed days and a 72% reduction in unplanned hospital admissions in the intervention group compared to the control group (2-sided test, significance level 0.05).

Aim 3

Analysis. This aim focuses on estimating and testing the mediating effects of family CG self-efficacy on their anxiety at Time T4 and other time points. The analysis will follow a standard (Baron-Kenny) approach of first testing the associations between intervention and the mediator (self-efficacy), and between self-efficacy and the outcome (anxiety) controlling for the intervention. If both associations are significant, the indirect effect of the mediator is estimated as the difference in the intervention effect on the anxiety before and after adjusting for the mediator.[109-111] The standard error of the indirect effect, used to construct a confidence interval, can be estimated using a marginal regression approach with standard generalized estimating equations software, or using a bootstrap approach.[111]

Power. If the effect size (difference in means of intervention vs. control groups divided by within-group standard deviation) is 0.40 for anxiety at T4, and is 0.50 for CG self-efficacy at T4 and the correlation of self-efficacy and anxiety at T4 is 0.40, the difference in means in anxiety after adjusting for the self-efficacy is reduced to an effect size of 0.20 *SDs* (i.e., the indirect effect of self-efficacy is 0.20, or 50% of the total). Simulations with n=10,000 replications showed in this scenario that the proposed approach had 81% power for testing that the indirect effect is zero (two-sided test, significance level 0.05). Increasing the indirect effect by increasing either the correlation or the effect of the intervention on self-efficacy results in higher power.

Aim 4

Analysis. This aim examines if patient illness factors, care demands, demographic factors, and/or use of mental health interventions during treatment moderate the relationship between the intervention and CG outcomes. Effects of potential modifiers of the treatment effect will be examined by including terms for the modifier by treatment interaction effect in the basic ANCOVA model used to test the primary hypothesis.

Power. Analyses for Aim 4 to examine moderating effects will be primarily exploratory in nature, since it is well-recognized that power for testing interaction effects is not high in trials that are powered to detect main effects, as is the case here.[112] When testing interaction of a binary factor occurring with frequency 0.5, power is 0.86 to detect an interactive effect size of 1.0 *SDs* (e.g., an intervention effect of 1.0 in one subgroup and an effect of 0.0 in the other), using a 2-sided test, significance level 0.05.

Aim 4a: Analyses for Aim 4a will examine if the SDH variables moderate the relationship between the intervention and caregiver outcomes. Effects of potential modifiers of the treatment effect will be examined by including terms for the SDH modifier by treatment interaction effect in the basic ANCOVA model used to test the primary hypothesis. The increase in enrollment from the extension study will provide additional power, as it is well-recognized that power for testing interaction effects is not high in trials that are powered to detect main effects, as was the case with the parent study. When testing interaction of a continuous SDH modifiers and the treatment, power is 0.81 to detect an interactive effect size of 0.40 standard deviations (SD) using a 2-sided test, significance level 0.05, for those measures that will be available in all subjects (e.g. Ohio Opportunity Index). For SDH measures that will only be available in the 96 extension study participants, we will be able to detect an interactive effect size of 0.59 at the same power and significance levels.

Aim 4b: Qualitative interviews will be audio recorded and transcribed, then verified for accuracy by research staff. Any identifiable information will be removed from transcripts, and each will be assigned a

study number. Deidentified data will be analyzed with NVIVO software using thematic analysis. First, the research team, including the PI, will read and reread 5 transcripts to develop a codebook using an inductive approach. Then, all transcripts will be coded by the research team using NVIVO to organize the data. Additional codes, and subsequently categories of codes will be identified. Clusters of categories converged into themes. Each transcript will be read and coded by three members of the research team for interrater reliability.

Aim 5

Analysis. We will assess costs associated with healthcare utilization in both intervention and control groups. Medicare reimbursement rates will be used to estimate costs regardless of the age or insurance of the participant. Using the DRG, diagnosis and procedure codes we will determine what Medicare "would have paid" for those services, and will use that as a proxy for cost. Cost of IV fluids will be estimated using wholesale acquisition cost. We will compute a healthcare utilization cost for each participant. Mean differences between the two groups will be analyzed using a two sample *t*-test for independent means. If necessary, data will be transformed to satisfy normality. In addition, we will describe costs associated with the intervention. Data regarding nurse time for preparation of the simulation and delivery of the intervention (in-person and phone contacts) will be collected prospectively during the study period. An hourly cost will be estimated according to hourly rates according to the Wage and Compensation Survey of the Bureau of Labor Statistics. Equipment costs will be measured. We will also determine costs related to the participants. CGs will be surveyed at each intervention contact (during radiation weeks 1 and 3, and at the end of radiation treatment) regarding: (1) any travel expenses for meetings with the intervention nurse and (2) time lost from work and activities due to the intervention, valued at 100% and 60% of the average hourly rate.

Power. A sample size of 81 in each group will provide 90% power of detecting a medium effect size (Cohen's *d*=0.5) difference between the two means. A two-tailed Type I error rate of 0.05 will be assumed.

In summary:
(1) For the power calculation, we focused on our primary hypothesis and outcome in Aim 1 to determine the sample size for our study (n=162); for the rest of other 4 Aims, we assessed the powers based on the sample size obtained in Aim 1. We showed that the proposed sample size will provide clinical meaningful effect size with enough statistical power for all the aims we planned to investigate;
(2) For model development and validation proposed in above aims, we will follow the general statistical model building strategy documented in detail in Harrell.[113] Some major aspects we will consider are: (a) dealing with missing data by multiple imputing of missing predictor values to make good use of partial subject information, (b) allowing for nonlinear predictor effects using regression splines, (c) adjusting the variance-covariance matrix for multiple imputation, (d) graphically interpreting the model using partial effect plots and nomograms, (e) quantifying the clinical utility (discrimination ability) of the model, and (f) internally validating the calibration and discrimination of the model using the bootstrap to estimate the model's likely performance on a new observation of samples from the same sample stream.

6.3 Stratification factors and intervention allocation plan for randomized studies.
Randomization will be done using the minimization stratified randomization technique (QMinim). Minimization is designed to balance pre-identified stratifying covariates across treatment assignments more effectively than simple randomization.[87-89] The covariates will be CG gender, CG age, and patient cancer type.

6.5 **Early stopping rules, if appropriate.** N/A

6.6 **Definition of and allowance in design for un-evaluable/ineligible participants.** N/A

7.0 REFERENCES

1. Hong F, Blonquist TM, Halpenny B, Berry DL. Patient-reported symptom distress, and most bothersome issues, before and during cancer treatment. *Patient Relat Outcome Meas*. 2016;7:127-135. doi: 10.2147/PROM.S95593.
2. Northouse LL, Katapodi MC, Song L, Zhang L, Mood DW. Interventions with family caregivers of cancer patients: Meta-analysis of randomized trials. *CA Cancer J Clin*. 2010;60(5):317-339. doi: 10.3322/caac.20081.
3. Kent EE, Rowland JH, Northouse L, et al. Caring for caregivers and patients: Research and clinical priorities for informal cancer caregiving. *Cancer*. 2016;122(13):1987-1995. doi: 10.1002/cncr.29939.
4. National Alliance for Caregiving, AARP Public Policy Institute. Caregiving in the U.S. 2015. Retrieved from http://www.caregiving.org/caregiving2015.
5. Ross S, Mosher CE, Ronis-Tobin V, Hermele S, Ostroff JS. Psychosocial adjustment of family caregivers of head and neck cancer survivors. *Support Care Cancer*. 2010;18(2):171-178. doi: 10.1007/s00520-009-0641-3.

6. van Ryn M, Sanders S, Kahn K, et al. Objective burden, resources, and other stressors among informal cancer caregivers: A hidden quality issue? *Psychooncology*. 2011;20(1):44-52. doi: 10.1002/pon.1703.
7. Havyer RD, van Ryn M, Wilson PM, Griffin JM. The effect of routine training on the self-efficacy of informal caregivers of colorectal cancer patients. *Support Care Cancer*. 2016. doi: 10.1007/s00520-016-3494-6.
8. Lambert SD, Girgis A, Lecathelinais C, Stacey F. Walking a mile in their shoes: Anxiety and depression among partners and caregivers of cancer survivors at 6 and 12 months post-diagnosis. *Support Care Cancer*. 2013;21(1):75-85. doi: 10.1007/s00520-012-1495-7.
9. Verdonck-de Leeuw IM, Eerenstein SE, Van der Linden, M H, Kuik DJ, de Bree R, Leemans CR. Distress in spouses and patients after treatment for head and neck cancer. *Laryngoscope*. 2007;117(2):238-241. doi: 10.1097/01.mlg.0000250169.10241.58.
10. Douglas SL, Daly BJ, Lipson AR. Relationship between physical and psychological status of cancer patients and caregivers. *West J Nurs Res*. 2016;38(7):858-873. doi: 10.1177/0193945916632531.
11. Jacobs JM, Shaffer KM, Nipp RD, et al. Distress is interdependent in patients and caregivers with newly diagnosed incurable cancers. *Ann Behav Med*. 2017. doi: 10.1007/s12160-017-9875-3.
12. Shinn EH, Valentine A, Jethanandani A, et al. Depression and oropharynx cancer outcome. *Psychosom Med*. 2016;78(1):38-48. doi: 10.1097/PSY.0000000000000256.
13. Bours MJ, van der Linden, B W, Winkels RM, et al. Candidate predictors of health-related quality of life of colorectal cancer survivors: A systematic review. *Oncologist*. 2016;21(4):433-452. doi: 10.1634/theoncologist.2015-0258.
14. Jeffries PR. A framework for designing, implementing, and evaluating simulations used as teaching strategies in nursing. *Nurs Educ Perspect*. 2005;26(2):96-103.
15. Grey M, Schulman-Green D, Knafl K, Reynolds NR. A revised self- and family management framework. *Nurs Outlook*. 2015;63(2):162-170. doi: 10.1016/j.outlook.2014.10.003.
16. Griffin JM, Meis LA, MacDonald R, et al. Effectiveness of family and caregiver interventions on patient outcomes in adults with cancer: A systematic review. *J Gen Intern Med*. 2014;29(9):1274-1282. doi: 10.1007/s11606-014-2873-2.
17. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin*. 2018;68(1):7-30. doi: 10.3322/caac.21442.
18. Sandstrom SK, Mazanec SR, Gittleman H, Barnholtz-Sloan JS, Tamburro N, Daly BJ. A descriptive, longitudinal study of quality of life and perceived health needs in patients with head and neck cancer. *J Adv Pract Oncol*. 2016;7(6):640-651. doi:10.6004/jadpro.2016.7.6.6.
19. Haisfield-Wolfe ME, McGuire DB, Krumm S. Perspectives on coping among patients with head and neck cancer receiving radiation. *Oncol Nurs Forum*. 2012;39(3):249. doi: 10.1188/12.ONF.E249-E257.
20. Rose P, Yates P. Quality of life experienced by patients receiving radiation treatment for cancers of the head and neck. *Cancer Nurs*. 2001;24:255-263.
21. Wells M. The hidden experience of radiotherapy to the head and neck: A qualitative study of patients after completion of treatment. *J Advanced Nursing*. 1998;28:840-848.
22. Haisfield-Wolfe ME, Brown C, Richardson M, Webster K. Variations in symptom severity patterns among oropharyngeal and laryngeal cancer outpatients during radiation treatment: A pilot study. *Cancer Nurs*. 2015;38(4):279-287. doi: 10.1097/NCC.0000000000000183.

23. Avery KN, Metcalfe C, Barham CP, Alderson D, Falk SJ, Blazeby JM. Quality of life during potentially curative treatment for locally advanced oesophageal cancer. *Br J Surg*. 2007;94(11):1369-1376. doi: 10.1002/bjs.5888.
24. Auperin A, Le Pechoux C, Rolland E, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. *J Clin Oncol*. 2010;28(13):2181-2190. doi: 10.1200/JCO.2009.26.2543.
25. Gift AG, Stommel M, Jablonski A, Given W. A cluster of symptoms over time in patients with lung cancer. *Nurs Res*. 2003;52(6):393-400.
26. Iyer S, Taylor-Stokes G, Roughley A. Symptom burden and quality of life in advanced non-small cell lung cancer patients in france and germany. *Lung Cancer*. 2013;81(2):288-293. doi: 10.1016/j.lungcan.2013.03.008.
27. Sodergren SC, Vassiliou V, Dennis K, et al. Systematic review of the quality of life issues associated with anal cancer and its treatment with radiochemotherapy. *Support Care Cancer*. 2015;23(12):3613-3623. doi: 10.1007/s00520-015-2879-2.
28. Joseph K, Vos LJ, Warkentin H, et al. Patient reported quality of life after helical IMRT based concurrent chemoradiation of locally advanced anal cancer. *Radiother Oncol*. 2016;120(2):228-233. doi: 10.1016/j.radonc.2016.06.020.
29. Knowles G, Haigh R, McLean C, Phillips H. Late effects and quality of life after chemo-radiation for the treatment of anal cancer. *Eur J Oncol Nurs*. 2015;19(5):479-485. doi: 10.1016/j.ejon.2015.02.007.
30. Sunesen KG, Norgaard M, Lundby L, et al. Long-term anorectal, urinary and sexual dysfunction causing distress after radiotherapy for anal cancer: A Danish multicentre cross-sectional questionnaire study. *Colorectal Dis*. 2015;17(11):230. doi: 10.1111/codi.13076.
31. Gilbert A, Ziegler L, Martland M, et al. Systematic review of radiation therapy toxicity reporting in randomized controlled trials of rectal cancer: A comparison of patient-reported outcomes and clinician toxicity reporting. *Int J Radiat Oncol Biol Phys*. 2015;92(3):555-567. doi: 10.1016/j.ijrobp.2015.02.021.
32. McMullen CK, Bulkley JE, Altschuler A, et al. Greatest challenges of rectal cancer survivors: Results of a population-based survey. *Dis Colon Rectum*. 2016;59(11):1019-1027. doi: 10.1097/DCR.0000000000000695.
33. Loos M, Quentmeier P, Schuster T, et al. Effect of preoperative radio(chemo)therapy on long-term functional outcome in rectal cancer patients: A systematic review and meta-analysis. *Ann Surg Oncol*. 2013;20(6):1816-1828. doi: 10.1245/s10434-012-2827-z.
34. Ozgen Z, Ozden S, Atasoy BM, Ozyurt H, Gencosmanoglu R, Imeryuz N. Long-term effects of neoadjuvant chemoradiotherapy followed by sphincter-preserving resection on anal sphincter function in relation to quality of life among locally advanced rectal cancer patients: A cross-sectional analysis. *Radiat Oncol*. 2015;10:4. doi: 10.1186/s13014-015-0479-4.
35. Reeve BB, Cai J, Zhang H, et al. Factors that impact health-related quality of life over time for individuals with head and neck cancer. *Laryngoscope*. 2016;126(12):2718-2725. doi: 10.1002/lary.26073.
36. Loorents V, Rosell J, Salgado Willner H, Borjeson S. Health-related quality of life up to 1 year after radiotherapy in patients with head and neck cancer (HNC). *Springerplus*. 2016;5(1):1. eCollection 2016. doi: 10.1186/s40064-016-2295-1.
37. Graham L, Wikman A. Toward improved survivorship: Supportive care needs of esophageal cancer patients, a literature review. *Dis Esophagus*. 2016;29(8):1081-1089. doi: 10.1111/dote.12424.

38. Mollica MA, Litzelman K, Rowland JH, Kent EE. The role of medical/nursing skills training in caregiver confidence and burden: A CanCORS study. *Cancer*. 2017. doi: 10.1002/cncr.30875.
39. Wittenberg E, Borneman T, Koczywas M, Del Ferraro C, Ferrell B. Cancer communication and family caregiver quality of life. *Behav Sci (Basel)*. 2017;7(1):10.3390/bs7010012. doi: E12.
40. Patterson JM, Rapley T, Carding PN, Wilson JA, McColl E. Head and neck cancer and dysphagia; caring for carers. *Psychooncology*. 2013;22(8):1815-1820. doi: 10.1002/pon.3226.
41. Penner JL, McClement S, Lobchuk M, Daeninck P. Family members' experiences caring for patients with advanced head and neck cancer receiving tube feeding: A descriptive phenomenological study. *J Pain Symptom Manage*. 2012;44(4):563-571. doi: 10.1016/j.jpainsymman.2011.10.016.
42. Houldin AD. A qualitative study of caregivers' experiences with newly diagnosedadvanced colorectal cancer. *Oncol Nurs Forum*. 2007;34(2):323-330. doi: C985497047376462.
43. Haj Mohammad N, Walter AW, van Oijen MG, et al. Burden of spousal caregivers of stage II and III esophageal cancer survivors 3 years after treatment with curative intent. *Support Care Cancer*. 2015;23(12):3589-3598. doi: 10.1007/s00520-015-2727-4.
44. Williams AL, Bakitas M. Cancer family caregivers: A new direction for interventions. *J Palliat Med*. 2012;15(7):775-783. doi: 10.1089/jpm.2012.0046.
45. Kayser K, Acquati C, Reese JB, Mark K, Wittmann D, Karam E. A systematic review of dyadic studies examining relationship quality in couples facing colorectal cancer together. *Psychooncology*. 2016. doi: 10.1002/pon.4339.
46. Haun MW, Sklenarova H, Brechtel A, Herzog W, Hartmann M. Distress in cancer patients and their caregivers and association with the caregivers' perception of dyadic communication. *Oncol Res Treat*. 2014;37(7-8):384-388. doi: 10.1159/000364885.
47. Wittenberg E, Ferrell B, Koczywas M, Del Ferraro C, Ruel NH. Pilot study of a communication coaching telephone intervention for lung cancer caregivers. *Cancer Nurs*. 2017. doi: 10.1097/NCC.0000000000000535.
48. Lapid MI, Atherton PJ, Kung S, et al. Cancer caregiver quality of life: Need for targeted intervention. *Psychooncology*. 2016;25(12):1400-1407. doi: 10.1002/pon.3960.
49. Longacre ML, Ridge JA, Burtness BA, Galloway TJ, Fang CY. Psychological functioning of caregivers for head and neck cancer patients. *Oral Oncol*. 2012;48(1):18-25. doi: 10.1016/j.oraloncology.2011.11.012.
50. Kim Y, Carver CS, Rocha-Lima C, Shaffer KM. Depressive symptoms among caregivers of colorectal cancer patients during the first year since diagnosis: A longitudinal investigation. *Psychooncology*. 2011. doi: 10.1002/pon.2100; 10.1002/pon.2100.
51. Pitceathly C, Maguire P. The psychological impact of cancer on patients' partners and other key relatives: A review. *Eur J Cancer*. 2003;39(11):1517-1524.
52. Vickery LE, Latchford G, Hewison J, Bellew M, Feber T. The impact of head and neck cancer and facial disfigurement on the quality of life of patients and their partners. *Head Neck*. 2003;25(4):289-296. doi: 10.1002/hed.10206.
53. Lee Y, Lin PY, Chien CY, Fang FM. Prevalence and risk factors of depressive disorder in caregivers of patients with head and neck cancer. *Psychooncology*. 2015;24(2):155-161. doi: 10.1002/pon.3619.
54. Richardson AE, Morton R, Broadbent E. Psychological support needs of patients with head and neck cancer and their caregivers: A qualitative study. *Psychol Health*. 2015:1-18. doi: 10.1080/08870446.2015.1045512.

55. Sklenarova H, Krumpelmann A, Haun MW, et al. When do we need to care about the caregiver? Supportive care needs, anxiety, and depression among informal caregivers of patients with cancer and cancer survivors. *Cancer*. 2015;121(9):1513-1519. doi: 10.1002/cncr.29223.
56. Hodges LJ, Humphris GM, Macfarlane G. A meta-analytic investigation of the relationship between the psychological distress of cancer patients and their carers. *Soc Sci Med*. 2005;60(1):1-12. doi: S0277953604001984.
57. Pinquart M, Sorensen S. Correlates of physical health of informal caregivers: A meta-analysis. *J Gerontol B Psychol Sci Soc Sci*. 2007;62(2):126. doi: 62/2/P126.
58. DuBenske LL, Gustafson DH, Namkoong K, et al. CHESS improves cancer caregivers' burden and mood: Results of an eHealth RCT. *Health Psychol*. 2014;33(10):1261-1272. doi: 10.1037/a0034216.
59. Porter LS, Keefe FJ, Garst J, et al. Caregiver-assisted coping skills training for lung cancer: Results of a randomized clinical trial. *J Pain Symptom Manage*. 2011;41(1):1-13. doi: 10.1016/j.jpainsymman.2010.04.014.
60. Mosher CE, Winger JG, Hanna N, et al. Randomized pilot trial of a telephone symptom management intervention for symptomatic lung cancer patients and their family caregivers. *J Pain Symptom Manage*. 2016;52(4):469-482. doi: S0885-3924(16)30173-7.
61. Sigalet E, Cheng A, Donnon T, et al. A simulation-based intervention teaching seizure management to caregivers: A randomized controlled pilot study. *Paediatr Child Health*. 2014;19(7):373-378.
62. Tofil NM, Rutledge C, Zinkan JL, et al. Ventilator caregiver education through the use of high-fidelity pediatric simulators: A pilot study. *Clin Pediatr (Phila)*. 2013;52(11):1038-1043. doi: 10.1177/0009922813505901.
63. Sullivan-Bolyai S, Bova C, Lee M, Johnson K. Development and pilot testing of a parent education intervention for type 1 diabetes: Parent education through simulation-diabetes. *Diabetes Educ*. 2012;38(1):50-57. doi: 10.1177/0145721711432457.
64. Eggenberger E, Heimerl K, Bennett MI. Communication skills training in dementia care: A systematic review of effectiveness, training content, and didactic methods in different care settings. *Int Psychogeriatr*. 2013;25(3):345-358. doi: 10.1017/S1041610212001664.
65. Mazanec SR, Flocke SA, Daly BJ. Health behaviors in family members of patients completing cancer treatment. *Oncol Nurs Forum*. 2015;42(1):54-62. doi: 10.1188/15.ONF.54-62.
66. Scholz U, Sniehotta FF, Silke Burkert D, Schwarzer R. Increasing physicial exercise levels: Age specific benefits of planning. *Journal of Aging and Health*. 2007;19(5):851-866.
67. Sniehotta FF, Schwarzer R, Scholz U, Schuz B. Action planning and coping planning for long-term lifestyle change: Theory and assessment. *European Journal of Social Psychology*. 2005;35:565-576.
68. Loerzel VW, Crosby WW, Reising E, Sole ML. Developing the tracheostomy care anxiety relief through education and support (T-CARES) program. *Clin J Oncol Nurs*. 2014;18(5):522-527. doi: 10.1188/14.CJON.522-527.
69. Hendrix CC, Bailey DE,Jr, Steinhauser KE, et al. Effects of enhanced caregiver training program on cancer caregiver's self-efficacy, preparedness, and psychological well-being. *Support Care Cancer*. 2015. doi: 10.1007/s00520-015-2797-3.
70. Bandura A. Self-efficacy: Toward a unifying theory of behavioral change. *Psychological Review*. 1977;84(2):191-215.
71. Porter LS, Keefe FJ, Garst J, McBride CM, Baucom D. Self-efficacy for managing pain, symptoms, and function in patients with lung cancer and their informal caregivers: Associations with symptoms and distress. *Pain*. 2008;137(2):306-315. doi: S0304-3959(07)00518-0.

72. Swore Fletcher BA, Dodd MJ, Schumacher KL, Miaskowski C. Symptom experience of family caregivers of patients with cancer. *Oncol Nurs Forum*. 2008;35(2):23. doi: 10.1188/08.ONF.E23-E44.
73. Dow KH, Ferrell BR, Haberman MR, Eaton L. The meaning of quality of life in cancer survivorship. *Oncol Nurs Forum*. 1999;26(3):519-528.
74. Bese NS, Hendry J, Jeremic B. Effects of prolongation of overall treatment time due to unplanned interruptions during radiotherapy of different tumor sites and practical methods for compensation. *Int J Radiat Oncol Biol Phys*. 2007;68(3):654-661. doi: S0360-3016(07)00504-4.
75. Freischlag K, Sun Z, Adam MA, et al. Association between incomplete neoadjuvant radiotherapy and survival for patients with locally advanced rectal cancer. *JAMA Surg*. 2017. doi: 10.1001/jamasurg.2017.0010.
76. Sreeraman R, Vijayakumar S, Chen AM. Correlation of radiation treatment interruptions with psychiatric disease and performance status in head and neck cancer patients. *Support Care Cancer*. 2013;21(12):3301-3306. doi: 10.1007/s00520-013-1907-3.
77. Fesinmeyer MD, Mehta V, Blough D, Tock L, Ramsey SD. Effect of radiotherapy interruptions on survival in medicare enrollees with local and regional head-and-neck cancer. *Int J Radiat Oncol Biol Phys*. 2010;78(3):675-681. doi: 10.1016/j.ijrobp.2009.08.004.
78. Keenan LG, O'Brien M, Ryan T, Dunne M, McArdle O. Assessment of older patients with cancer: Edmonton frail scale (EFS) as a predictor of adverse outcomes in older patients undergoing radiotherapy. *J Geriatr Oncol*. 2016. doi: S1879-4068(16)30171-0.
79. Sterba KR, Zapka J, Cranos C, Laursen A, Day TA. Quality of life in head and neck cancer patient-caregiver dyads: A systematic review. *Cancer Nurs*. 2016;39(3):238-250. doi: 10.1097/NCC.0000000000000281.
80. Houldin AD. A qualitative study of caregivers' experiences with newly diagnosedadvanced colorectal cancer. *Oncol Nurs Forum*. 2007;34(2):323-330. doi: C985497047376462.
81. Franklin AE, Lee CS. Effectiveness of simulation for improvement in self-efficacy among novice nurses: A meta-analysis. *J Nurs Educ*. 2014;53(11):607-614. doi: 10.3928/01484834-20141023-03.
82. Shin S, Park JH, Kim JH. Effectiveness of patient simulation in nursing education: Meta-analysis. *Nurse Educ Today*. 2015;35(1):176-182. doi: 10.1016/j.nedt.2014.09.009.
83. Hassan SJ, Weymuller EA,Jr. Assessment of quality of life in head and neck cancer patients. *Head Neck*. 1993;15(6):485-496.
84. Mazanec SR, Sattar A, Delaney CP, Daly BJ. Activation for health management in colorectal cancer survivors and their family caregivers. *West J Nurs Res*. 2016;38(3):325-344. doi: 10.1177/0193945915604055.
85. Mazanec SR, Miano S, Baer L, Campagnaro EL, Sattar A, Daly BJ. A family-centered intervention for the transition to living with multiple myeloma as a chronic illness: A pilot study. *Applied Nursing Research*. 2017;doi:10.1016/j.apnr.2017.03.003.
86. Daly BJ, Douglas SL, Gunzler D, Lipson AR. Clinical trial of a supportive care team for patients with advanced cancer. *J Pain Symptom Manage*. 2013;46(6):775-784. doi: 10.1016/j.jpainsymman.2012.12.008.
87. Altman DG, Schulz KF, Moher D, et al. The revised CONSORT statement for reporting randomized trials: Explanation and elaboration. *Ann Intern Med*. 2001;134(8):663-694. doi: 200104170-00012.
88. Taves DR. The use of minimization in clinical trials. *Contemp Clin Trials*. 2010;31(2):180-184. doi: 10.1016/j.cct.2009.12.005.

89. Lin Y, Zhu M, Su Z. The pursuit of balance: An overview of covariate-adaptive randomization techniques in clinical trials. *Contemp Clin Trials*. 2015;45(Pt A):21-25. doi: 10.1016/j.cct.2015.07.011.
90. Northouse LL, Rosset T, Phillips L, Mood D, Schafenacker A, Kershaw T. Research with families facing cancer: The challenges of accrual and retention. *Res Nurs Health*. 2006;29(3):199-211. doi: 10.1002/nur.20128.
91. Applebaum AJ, Breitbart W. Care for the cancer caregiver: A systematic review. *Palliat Support Care*. 2013;11(3):231-252. doi: 10.1017/S1478951512000594.
92. Haun J, Noland-Dodd V, Varnes J, Graham-Pole J, Rienzo B, Donaldson P. Testing the BRIEF health literacy screening tool. *Fed Pract*. 2009;26(12):31.
93. Haun J, Luther S, Dodd V, Donaldson P. Measurement variation across health literacy assessments: Implications for assessment selection in research and practice. *J Health Commun*. 2012;17 Suppl 3:141-159. doi: 10.1080/10810730.2012.712615.
94. DeWalt DA, Callahan LF, Hawk VH, et al. *Health literacy universal precautions toolkit, AHRQ publication no. 10-0046-EF.* Rockville, MD: Agency for Healthcare Research and Quality; 2010.
95. Cella D, Riley W, Stone A, et al. The patient-reported outcomes measurement information system (PROMIS) developed and tested its first wave of adult self-reported health outcome item banks: 2005–2008. *Journal of Clinical Epidemiology*. 2010;63:1179-1194. doi:10.1016/l.jclinepi.2010.04.011.
96. Ward WL, Hahn EA, Mo F, Hernandez L, Tulsky DS, Cella D. Reliability and validity of the functional assessment of cancer therapy-colorectal (FACT-C) quality of life instrument. *Qual Life Res*. 1999;8(3):181-195.
97. Darling G, Eton DT, Sulman J, Casson AG, Celia D. Validation of the functional assessment of cancer therapy esophageal cancer subscale. *Cancer*. 2006;107(4):854-863. doi: 10.1002/cncr.22055.
98. List MA, D'Antonio LL, Cella DF, et al. The performance status scale for head and neck cancer patients and the functional assessment of cancer therapy-head and neck scale. A study of utility and validity. *Cancer*. 1996;77(11):2294-2301. doi: AID-CNCR17>3.0.CO;2-S.
99. Merluzzi TV, Philip EJ, Vachon DO, Heitzmann CA. Assessment of self-efficacy for caregiving: The critical role of self-care in caregiver stress and burden. *Palliat Support Care*. 2011;9(1):15-24. doi: 10.1017/S1478951510000507.
100. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the eastern cooperative oncology group. *Am J Clin Oncol*. 1982;5(6):649-655.
101. Roila F, Lupattelli M, Sassi M, et al. Intra and interobserver variability in cancer patients' performance status assessed according to karnofsky and ECOG scales. *Ann Oncol*. 1991;2(6):437-439.
102. Borrelli B, Sepinwall D, Ernst D, et al. A new tool to assess treatment fidelity and evaluation of treatment fidelity across 10 years of health behavior research. *J Consult Clin Psychol*. 2005;73(5):852-860. doi: 10.1037/0022-006X.73.5.852.
103. Farran CJ, Etkin CD, McCann JJ, Paun O, Eisenstein AR, Wilbur J. Role of technology in supporting quality control and treatment fidelity in a family caregiver clinical trial. *West J Nurs Res*. 2011;33(7):953-978. doi: 10.1177/0193945910394453.
104. Cella DF, Bonomi AE, Lloyd SR, Tulsky DS, Kaplan E, Bonomi P. Reliability and validity of the functional assessment of cancer therapy-lung (FACT-L) quality of life instrument. *Lung Cancer*. 1995;12(3):199-220. doi: 016950029500450F.

105. Cella D. The functional assessment of cancer therapy-lung and lung cancer subscale assess quality of life and meaningful symptom improvement in lung cancer. *Semin Oncol*.2004;31(3 Suppl 9):11-15. doi: S0093-7754(04)00202-7.
106. Cohen J. *Statistical power analysis for the behavioral sciences.* 2nd ed. Hillsdale, New Jersey: Lawrence Erlbaum Associates; 1988.
107. Greene WH. Accounting for excess zeros and sample selection in Poisson and negative binomial regression models. *Department of Economics, Stern School of business, New York University, New York*. 1994;NYU Working Paper No. EC-94-10.
108. Lambert D. Zero-inflated Poisson regression with an application to defects in manufacturing. *Technometrics*. 1992;34:1-14.
109. Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: Conceptual, strategic, and statistical considerations. *Journal of Personality and Social Psychology*. 1986;51(6):1173-1182.
110. MacKinnon DP, Lockwood CM, Hoffman JM, West SG, Sheets V. A comparison of methods to test mediation and other intervening variable effects. *Psychol Methods*. 2002;7(1):83-104.
111. Schluchter MD. Flexible approaches to computing mediated effects in generalized linear models: Generalized estimating equations and bootstraping. *Multivariate Behavioral Research*. 2008;43(2):268-288.
112. Lachenbruch PA. A note on sample size computations for testing interactions. *Statistics in Medicine*. 1988;7:467-469.
113. Harrell Jr. FE. *Regression modeling strategies: With applications to linear models, logistic regression, and survival analysis* (Springer series in statistics). 2001. New York: Springer.
114. Webster K, Cella D, Yost K. The Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System: properties, applications, and interprestation. *Health and Quality of Life Outcomes*. 2003; 1:79.
115. Cella DF et al. The Functional Assessment of Cancer Therapy Scale: development and validation of the general measure. *Journal of Clinical Oncology*. 1993; 11:570-579.

8.0 APPENDICES

Appendix A. Instruments (attached)
Appendix B. Study brochure for caregivers