**Study Title:** Prepare to Care, A Supported Self-Management Intervention for Head and Neck Cancer Caregivers

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**Background, Rationale and Context**

In 2016, 62,000 people are expected to be diagnosed with HNC in the United States; over 13,000 people are expected to die from the disease [1]. Recurrence rates are high (20%) relative to other cancer diagnoses [2, 3]. Treatment is complex and often includes radiotherapy (RT) for 5 days a week over 6-7 weeks, sometimes with chemotherapy and surgery [4]. Patients experience significant side effects that impede core aspects of daily life, presenting challenging care tasks for informal caregivers. One of the most notable side effects is dysphagia, affecting as many as 75% of patients and contributing to rapid weight loss, malnutrition, and dehydration [5, 6]. Other life altering side effects can include pain, dry mouth, and difficulty hearing and speaking [7, 8]. Caregivers must often engage in special food preparation (e.g., pureeing food) and tube management for patients [9, 10], as well as more traditional informal caregiving tasks such as providing emotional support, managing medical appointments and insurance claims, and providing hands-on medical care with little to no training [11, 12]. Patients may be stigmatized due to tobacco and alcohol use, or a human papilloma virus (HPV) association (major contributing factors in the disease etiology) or treatment-related disfigurement [13]. Concurrently, patients may also experience embarrassment and isolation [10]. Not surprisingly, HNC patients have a high incidence of psychological distress and report higher care needs relative to other cancer patients [14, 15].

Approximately 3.5 million people provide care for patients with cancer [16]. Although caregiving can be personally rewarding [17], studies have overwhelmingly demonstrated a negative impact on cancer caregivers, including poor quality of life, risk of clinical depression, sleep disturbance, fatigue, pain, loss of physical strength, loss of appetite, and weight loss [18-20]. Studies focused on HNC caregivers are sparse. The limited literature describes a high prevalence of agoraphobia (anxiety disorder) [21], depression [22], and a high fear of patient cancer recurrence [23], with caregivers reporting poorer psychological health compared to patients and the general population [24]. Our research has shown that

during patient RT treatment, HNC caregivers experience increased schedule burden, decreased esteem, poorer self-reported health, and an abnormal cortisol response (dysregulated cortisol slope) from treatment initiation to five weeks into patient's radiotherapy (RT) [25]. HNC caregivers have unmet informational needs and desire psychological support, self-help groups, and help with coping strategies [26-28]. In one study, most spouses of laryngectomized cancer patients desired to learn relaxation methods [29]. Such services can be addressed in a psycho-educational (education pertaining to emotional well-being) and stress management intervention. Our own work has highlighted high interest in wellness programs in HNC caregivers [30].

Psychosocial interventions for informal caregivers have successfully improved burden, depression, subjective well-being, perceived caregiver satisfaction, and ability/knowledge, with multiple component interventions more effectively reducing burden versus single component interventions [31]. However, HNC caregivers have been neglected. One study[32] did evaluate the feasibility of a one-day 6-hour workshop to facilitate coping among HNC patients and family members, but the workshop was not restricted to those providing care. Although participants were highly satisfied with the intervention, only 19% of families approached agreed to participate. Barriers to recruitment and participation included a lack of interest in seeking family support or logistical barriers. Our proposed study will overcome these barriers by providing caregivers with an easily accessible intervention that offers several choices designed to meet their specific preferences.

A burgeoning area of research focuses on supported self-management (SSM) interventions. In SSM interventions, the recipient uses self-directed educational materials to learn information and strategies to manage emotions and promote healthy behaviors typically associated with chronic diseases, such as cancer, with the support of a health care provider [33, 34]. Accordingly, SSM interventions offer an ideal platform for delivery of psycho-education and stress management skills building. SSM interventions can be low cost, reduce health care utilization, and have greater dissemination potential [33, 35]. Further, SSM interventions can be used according to the participant's preferences for place and time and combat logistical barriers to in-person delivered interventions. As such, they may be especially attractive to HNC caregivers navigating the hectic RT treatment period. To date, SSM interventions have largely been applied in cancer patients, particularly in more common cancer types; they successfully improve fatigue, depression, anxiety, and overall QOL [36]. One study did report feasibility and acceptability of a SSM intervention for caregivers of blood and marrow transplant cancer survivors after treatment, but caregivers wished they had received the intervention earlier during patient treatment [37]. Similarly, our preliminary data demonstrate that HNC caregivers desire wellness programs during patient treatment.

Salivary cortisol response is an important indicator of stress and is helpful for evaluating efficacy of stress-management trials. Cortisol is a glucocorticoid and a biomarker of stress that is released from the hypothalamic pituitary adrenal (HPA) axis [38]. Studies within the psychoneuroendocrinology literature have demonstrated a relationship between psychological distress and cortisol response. For example, studies have demonstrated an association between cortisol and depressive symptoms[39, 40], post-traumatic stress disorder symptoms[41], and anxiety [42]. Additionally, other similar psychosocial interventions have demonstrated changes in cortisol response [43, 44].

## Objectives

**Aim 1:** To assess feasibility (accrual, participation, and retention) and acceptability of a supported self-management intervention for psycho-education and stress management skills building designed for informal caregivers (Intervention Group, n=20; Waitlist Control Group, n=20) of HNC patients undergoing RT.

**Aim 2a:** To obtain preliminary data on caregiver intermediate (self-efficacy for (a) coping with cancer and (b) abbreviated progressive muscle relaxation) and outcome variables (burden, psychological distress, quality of life) in intervention caregivers and waitlist control caregivers at the start of radiation (T1), end of radiation (T2), and 6-weeks post-radiation (T3).

**Aim 2b:** To compare intermediate (self-efficacy for (a) coping with cancer and (b) abbreviated progressive muscle relaxation) and outcome variables (burden, psychological distress, quality of life) between intervention caregivers and waitlist control caregivers at T1, T2, and T3.

> ***Hypothesis****: (Aim 2a) Intermediate and outcome variables will improve in intervention caregivers post-intervention compared to pre-intervention and (Aim 2b) intervention caregivers will have better intermediate (higher self-efficacy for a) coping with cancer, and b) abbreviated progressive muscle relaxation) and outcome variables (less burden, less psychological distress, higher QOL) at T2 compared to waitlist control caregivers.*

**Aim 3:** To obtain preliminary data on caregiver cortisol response (cortisol slope, cortisol awakening response, area under the curve, and intra-individual cortisol variability) at T1 – T3 in intervention caregivers and waitlist control caregivers.

> ***Hypothesis:*** *Intervention caregivers will demonstrate a more normal (steeper) diurnal cortisol rhythm (slope) at T2 compared to waitlist control caregivers.*

**Aim 4:** To refine intervention procedures and materials for future studies by examining: a) qualitative data from caregivers and interventionist notes and b) quantitative data regarding module utilization.

## Methods and Measures

**Design:** Recruitment will include both patients and caregivers, although patients are not receiving the intervention. We will recruit 40 caregivers (20 intervention caregivers; 20 waitlist control caregivers) of patients with head and neck cancer (HNC) referred for radiotherapy (RT) and their informal caregivers, before or at the start of patient RT. After baseline assessment, caregivers will be randomized at the time of registration using a randomization scheme uploaded into the registration system, The randomization scheme will be developed by the statistician. Block sizes will be chosen randomly to ensure that future assignments cannot be inferred from previous ones. Caregivers will be randomized to receive either a psycho-educational and stress management skills building intervention offered in a SSM format, accessible in hard copy and online, with iPads linking to study materials available during daily patient RT sessions, or a waitlist control group. Caregivers will complete assessments at the start of RT (T1), end of RT (T2), and 6-weeks post-RT (T3). Waitlist control caregivers will be offered *Prepare to Care* materials (without support from the study interventionist) after final assessment at T3. Patient participation is optional and restricted to providing consent for study staff to abstract information on clinical information from their medical record. If a patient declines to participate in the study, caregivers will be asked to report the patient clinical information collected at T1. See Appendix A for study schema.

**Setting:** Participants will be recruited from the outpatient radiation clinics at the Comprehensive Cancer Center of Wake Forest University and the Lexington Medical Center or by mail. Participants will meet with the study interventionist at the radiation clinic or by telephone, and have the option to access intervention materials from the study website using i-Pads that remain at the clinic or accessing the website away from the clinic. The self-management intervention is designed so that caregivers can utilize the kit in a preferred location (e.g., at home) and time.

**Subjects selection criteria**

**Caregivers**

- **Inclusion Criteria**
  (1) providing the majority of the informal (unpaid) care during RT for a patient meeting inclusion criteria (see below) and participating in study, and (2) ≥18 years of age.
- **Exclusion Criteria**
  (1) has a current cancer diagnosis, (2) cannot read/ communicate in English, (3) Caregivers who have an endocrine disorder (e.g., diabetes and thyroid disorders), or is currently taking a steroid-based medication will not be eligible to participate in the saliva portion of the study.

**Care-recipients**

- **Inclusion Criteria**
- (1) has a new or recurrent AJCC stage I-IV squamous cell carcinoma of the upper aerodigestive tract (including lip/oral cavity, nasopharnyx, salivary gland, oropharynx, hypopharynx, paranasal sinus, and larynx cancers), (2) has planned external beam radiotherapy (+/- chemotherapy) for 6-7 weeks, (3) ≥18 years of age, and (4) has an informal (unpaid) caregiver during RT who is participating in study.
- **Exclusion Criteria**
  (1) cannot read/ communicate in English.

- **Sample Size**
  The sample size is based on feasibility (Aim 1). Our primary feasibility measures are participation and retention rates. About 110 patients present to our outpatient radiation clinic for treatment per year (9/mo). Based on previous experience, we expect approximately 75% of patients (n = 82) will have a caregiver and at least 75 patient-caregiver dyads will meet eligibility criteria (6/mo). With an estimated participation rate (consistent with PI's experience) of 70%, we expect to recruit 40 patient-caregiver dyads within 8-10 months. If we approach 56 participants to recruit 40, we will be able to estimate the participation rate within +/- 12% using a two-sided 95% confidence interval; thus, we can be 95% confident that the true recruitment rate would be between 59% and 83%, which would support that the study is feasible. With 40 participants we can estimate the retention rate within +/- 12%. If the observed retention rate is 80%, we can be 95% confident that the true rate is between 67% and 92%, which would indicate a feasible study.

**Interventions and Interactions**

After recruitment and randomization, caregivers in the intervention group will meet with the study interventionist to review the intervention.

**Overview of Intervention** (see Table 1)
The multi-component intervention (or kit), *Prepare to Care*, includes:
1) brief introduction video on a DVD,
2) binder including eight workbook modules offered in hard copy, and
3) CD with audio instructions to facilitate Progressive Muscle Relaxation (PMR) Training (included in module 8).

**Modules**

The first two modules provide cancer education and a list of supportive resources; modules 3-8 focus on stress management skills to enhance caregiver coping during RT (Table 1). Each module includes an introduction and rationale for the topic, strategies to overcome relevant challenges, and a weekly exercise. PMR training (in module 8) teaches caregivers to identify muscle tension signals and to use the signals as cues to trigger a relaxation response [45]. The breadth of topics and succinct modules are intended to provide a balance between addressing a comprehensive set of challenges and preventing participant burden.

| **Table 1. *Prepare to Care* Kit Components** | |
|---|---|
| **Module: Topic** | **Description** |
| **DVD Introduction** | Brief introduction to the intervention: rationale and how to use the kit |
| **Educational** | |
| **1: Cancer Education** | Information about HNC, RT (+/- chemotherapy), side effects, and managing patient side effects |
| **2: Using Your Resources** | Information linking caregivers to supportive resources available within a) the CCCWFU, b) Forsyth County, and c) the internet |
| **Stress Management Skills** | |
| **3: Managing Time** | Managing a busy schedule, including recognizing competing outside demands & prioritizing |
| **4: Seeking/ Accepting Support** | Importance of social support, learning to identify supporters and ask for help when needed; |
| **5: Communicating with Others** | Strategies to optimize communication with provider, patient, and other friends/family members |
| **6: Healthy Behaviors** | Importance of healthy behaviors (diet, physical activity, sleep) as a cancer caregiver |
| **7: Positive Coping** | Learning to identify and re-frame negative thoughts[46] |
| **8: Muscle Relaxation** | Importance of engaging in relaxation; Also includes a CD with audio instructions for PMR |

**Intervention Delivery and Participation**: *Prepare to Care* kit materials are offered in a blended delivery format. To maximize intervention engagement, in addition to the intervention kit, modules are also accessible on a study website and iPads linking directly to the website will be available for use at the RT clinic. Modules 3-8 are designed to take 30- 45 minutes each, and each module does not have to be completed in one sitting; caregivers are instructed to complete at least one module per week and re-visit previous modules as needed. Each week, caregivers will complete a needs assessment with the interventionist to help direct them to relevant modules. However, if new challenges present during the week, caregivers are encouraged to use other pertinent modules. This preference-based approach empowers caregivers to build skills to address current challenges. The workbook will include a time log for caregivers to record the date, modules utilized, and times for starting and ending each module. Waitlist control caregivers will not meet with the study interventionist when provided with the intervention.

**Interactions with Interventionist:** During weekly interventionist sessions (estimated to take 10-30 min), the interventionist will complete needs assessments, as discussed above, and inquire about modules used the prior week, assist in overcoming potential barriers to participation, and assist with incomplete activities, if desired. These sessions will occur weekly at the RT clinic when caregivers typically accompany the patient, capitalizing on the existing infrastructure for treatment schedules and thereby reducing participant burden. When necessary, sessions can also be completed via telephone. The interventionist will also send weekly email and/or text reminders each Wednesday to engage with caregivers and support adherence. The interventionist has extensive experience interacting with participants in psychosocial/ behavioral research studies and will be trained in intervention content. Waitlist control caregivers will not meet with the study interventionist when provided with the intervention.

**Outcome Measure(s)**

See Table 2 for the assessment plan. For caregivers, sociodemographics and caregiving characteristics will be collected at recruitment. We will collect basic demographics and patient clinical information via medical chart review at recruitment and after RT. At T1, T2 and T3, caregivers will complete instruments at the RT clinic (or by phone, mail, or email using REDCAP) to assess intermediate (self-efficacy in (a) coping with cancer and (b) PMR and outcome variables (burden, psychological distress, quality of life). Caregivers may also self-collect saliva samples (see additional details below). Between T2 and T3, we will assess intervention caregivers' overall acceptability of the intervention with a quantitative survey developed for the study and semi-structured interviews (lasting approximately 30 minutes to an hour) to explore factors influencing overall acceptability. Caregivers will be asked what they liked and disliked about content and delivery of intervention materials, weekly sessions with the interventionist, and email/text reminders. Interviews will be recorded and transcribed, and qualitative data will be managed using Microsoft Excel.

**Salivary Cortisol:** Caregiver participants who do not have an endocrine disorder (e.g., diabetes and thyroid disorders), and are not currently taking a steroid-based medication are eligible for the saliva portion of the study. Materials for saliva collection will be mailed or distributed to eligible participants in person at the start of the study. Participants will collect saliva samples three times a day (at awakening, 30 minutes post-awakening, and bedtime) for two consecutive days following T1, T2, and T3. Saliva samples are collected by placing a cotton roll under the tongue for approximately 1-2 minutes which is subsequently stored in a plastic tube and refrigerated. Participants will be instructed to refrain from eating, drinking, smoking, brushing their teeth, using mouthwash, or engaging in exercise or similar physical activity for 30 minutes prior to saliva collection. Participants will be provided with saliva collection diaries to record compliance to these behaviors as well as the time in which their saliva samples were collected. After all six samples have been collected at each time point (T1, T2, T3), participants will return their samples in person at the radiation clinic (T1) or by mail (T2 & T3) using pre-paid postage to return their samples and saliva collection diaries to the Wake Forest study site. Once received at the study site, all samples will be immediately centrifuged to remove the saliva from the adsorbent swabs, discarding the swabs and swab holder. The collection tube containing the saliva will be weighed. The saliva will then be transferred in approximately equal aliquots to freezer storage tubes before freezing. All storage tubes will be labeled using a barcode. Sample aliquots will be stored in freezer boxes at -80° C until assayed. The location of each group of samples in the freezer will be recorded in the sample database.

Samples will be assayed in duplicate at Wake Forest using The Salimetrics® Cortisol Enzyme Immunoassay Kit (State College, PA). The saliva storage tubes will be labeled with a barcode, at no time in the testing process are samples identified by name of subject. On the day of analysis, samples are thawed at room temperature (20 to 22°C), centrifuged (1500 x g) for 15 minutes and assayed. The test used 25 µL of saliva per determination, has a lower limit of sensitivity of 0.003 µg/dL, standard curve range from 0.012 µg/dL to 3.0 µg/dL, an average intra-assay coefficient of variation of 3.5% and an average inter- assay coefficient of variation of 5.1%. Method accuracy determined by spike and recovery averaged 100.8% and linearity determined by serial dilution averaged 91.7%. Values from matched serum and saliva samples show the expected strong linear relationship, $r(47) = 0.91$, $p < 0.0001$.

Samples are returned to the freezer upon completion of pipetting. Assay data are reviewed by the supervisor and samples needing to be retested are identified. Samples needing retesting are again thawed, analyzed and refrozen. After assays are complete, samples will be stored for up to three years and then disposed of per applicable waste handling regulations.

**Table 2. Assessment Plan**

| Assessment | Time | Description |
|---|---|---|
| Caregiver sociodemographics | T1 | Age, gender, race/ethnicity, education, employment, income, marital status, insurance status |
| Patient clinical information | T1, T3 | AJCC Stage, location of tumor, prior cancer (yes/no), time since surgery, new or recurrent diagnosis, chemotherapy (yes/no), # of weeks of RT, patient response to treatment (T3 only) |
| Caregiving characteristics | T1; T2;T3 | Living with patient (yes/no), relationship to patient (T1 only), hours of daily care |
| **Aim 1** | | |
| Feasibility | | |
| Participation | Study duration | Proportion of eligible participants who agreed to participate |
| Retention | Study duration | Number of participants who completed the T2 visit divided by the number who agreed to participate |
| Accrual | Study duration | Number of caregivers who agreed to participate divided by the number of months of recruitment |
| Acceptability | | |
| Quantitative survey; Qualitative interview (intervention caregivers only)[1] | Anytime from T2-T3 | 15-item quantitative survey developed for study to assess how much caregivers liked different aspects of the intervention; Qualitative interviews to further explore factors associated with overall acceptability. |
| **Aims 2a & 2b** | | |
| Intermediate Outcomes | | |
| Self-efficacy in coping with cancer Caregiver Inventory (CI)[47] | T1; T2; T3 | 21-item instrument assessing caregivers' perceived self-efficacy for coping with cancer (managing medical information, caring for care recipient, caring for oneself, managing difficult interactions/emotions); demonstrated validity and reliability. |
| Self-efficacy in PMR | T1; T2; T3 | 3-item instrument developed for study to evaluate self-efficacy in PMR. |
| Outcome Variables | | |
| (CES-D) [48] | T1; T2; T3 | 20-item instrument how often over the past week they experienced symptoms associated with depression, such as restless sleep, poor appetite, and feeling lonely. The CESD has been widely used in caregiver populations. |
| (PROMIS Emotional Distress Anxiety Short Form- 8a)[49] | T1; T2; T3 | Brief 8-item assessment of anxiety over the past week. |
| Caregiver burden<br>• Caregiver Reaction Assessment (CRA) [50] | T1; T2; T3 | 24-item instrument assessing positive and negative aspects of caregiving (esteem, lack of family support, finances, schedule, and health). The CRA has been tested in cancer caregivers; demonstrated validity and reliability [50, 51]. |
| QOL<br>• Caregiver Quality of Life Index-Cancer (CqoL-Canc) [52] | T1; T2; T3 | 35-item instrument assessing dimensions of caregiver QOL (burden, disruptiveness, positive adaptation, financial concerns). The Cqol-Canc has demonstrated validity and reliability [51, 52]. |
| **Aim 3** | | |
| Salivary Cortisol Collection (for eligible caregivers only) | T1; T2; T3 | Collected three times a day (at awakening, 30 minutes post-awakening, and bedtime) for two consecutive days following T1, T2, and T3. Saliva samples are collected by placing a cotton roll under the tongue for approximately 1-2 minutes which is subsequently stored in a plastic tube and refrigerated. |
| **Aim 4** | | |
| Modules Utilized (intervention caregivers only) | Study duration | Frequency of intervention modules utilized; retrieved from caregiver logs |
| Interventionist notes | Study duration | Process notes regarding intervention implementation |

## Analytical Plan

The analyses will provide quantitative data on participation, retention, and accrual, and estimates of the effect size of the intervention for intermediate and outcome variables. This information, along with ratings of acceptability and qualitative analyses, will allow us to refine the protocol for a larger study.
**Aim 1:** To assess feasibility (accrual, participation, and retention) and acceptability of a supported self-management intervention for psycho-education and stress management skills building designed for

informal caregivers (Intervention Group, n=20; Waitlist Control Group, n=20) of HNC patients undergoing RT.

Accrual rate will be defined as the number of caregivers who agreed to participate divided by the number of months of recruitment. Participation rate will be defined as the percent of eligible participants who agreed to participate. Retention rate will be defined as the number of participants who completed T3 measures divided by the number who consented to participate. Mean accrual rate, participation rate, and retention rates and their associated 95% confidence intervals (CI) will be estimated.

Acceptability will be summarized quantitatively and qualitatively. Descriptive statistics will summarize participants' overall rating of acceptability; ANOVA and regression models will examine if acceptability varies by demographic, caregiving, or patient characteristics. A codebook for analyzing the qualitative interviews will be developed using a thematic analysis procedure, facilitating coding into discrete categories. Interviews will be coded by at least two raters and discrepancies will be discussed until consensus is reached. Frequency counts will be calculated for themes pertinent to caregivers' likes/dislikes.

**Aim 2a:** To obtain preliminary data on caregiver intermediate (self-efficacy for (a) coping with cancer and (b) abbreviated progressive muscle relaxation) and outcome variables (burden, psychological distress, quality of life) in intervention caregivers and waitlist control caregivers at the start of radiation (T1), end of radiation (T2), and 6-weeks post-radiation (T3).

**Aim 2b:** To compare intermediate (self-efficacy for (a) coping with cancer and (b) abbreviated progressive muscle relaxation) and outcome variables (burden, psychological distress, quality of life) between intervention caregivers and waitlist control caregivers at T1, T2, and T3.

We will use a mixed effects model with a random subject effect and time (T1,T2,T3), group, and a group by time interaction to model change in the intermediate variables (self-efficacy for (a) coping with cancer (CI) and (b) PMR) and outcome variables (burden (CRA), depression (CESD), anxiety (PROMIS Short Form-Anxiety 7a), and QOL (CQoL-Canc), by group from T1 to T2 to T3). We will use linear contrasts to compare the intervention to the control group at T1, T2, and T3. In exploratory analyses we will model the relationship between each outcome and the intermediate variable, by including the intermediate variable as a fixed effect in the model. These results are exploratory due to concurrent measurement with outcome variables; in future studies we would capture potential mediators at an intermediate time point.

**Aim 3:** To obtain preliminary data on caregiver cortisol response (cortisol slope, cortisol awakening response, area under the curve, and intra-individual cortisol variability) at T1 – T3 in intervention caregivers and waitlist control caregivers.

**Analysis Plan:** Analyses for Aim 3 will be conducted using data from caregivers who were not excluded from the saliva portion of the study. Several summary measures will be derived from the three daily cortisol values, including the mean levels at each time, the mean cortisol awakening response (CAR – change in cortisol from awakening to 30 minutes), the area under the curve (AUC), the diurnal slope (change in cortisol between awakening and bedtime), and the intraindividual cortisol variability, which will be estimated using the methods as described in Sannes et al.[53] to assess group differences in cortisol parameters. We will use a mixed model to evaluate differences between the groups in these parameters at times T1 and T2 and T3. For a subset of the sample who completed measures on intermediate and outcome variables and cortisol, in exploratory models, we will include the cortisol summary measures as predictor variables in the models described for Aim 2 above.

**Aim 4:**To refine intervention procedures and materials for future studies by examining: a) qualitative data from caregivers and interventionist notes and b) quantitative data regarding module utilization.

We anticipate that participants who more fully utilize the modules may derive a greater benefit than those who do not. We will include utilization as an interaction term in the mixed effect model to assess this hypothesis in an exploratory analysis. This information will help us to refine the protocol, but will not be fully powered to quantify effects. Quantitative and qualitative findings will be synthesized, along with interventionist implementation notes, and included in a final report. The report will be used to determine potential refinement in the recruitment process, content of intervention materials, delivery of intervention components, and email/text reminders. The report will be presented to advisory panel members who will participate in making final decisions for refinement.

## Human Subjects Protection

All team investigators have completed their institution's courses for Protection of Human Research Subjects and will maintain up to date certification throughout the study period.

### Human Subject Involvement and Characteristics.

Caregiver involvement. This study will enroll 40 head and neck cancer (HNC) caregivers recruited from the outpatient radiation clinics at the Comprehensive Cancer Center of Wake Forest University (CCCWFU) and the Lexington Medical Center or by mail. Caregivers will be recruited before or at the start of patient RT and participation will end 6 weeks after patients complete RT. Caregivers will participate in either an intervention group that provides psycho-education and teach stress management skills during the patient's radiotherapy (RT) treatment or a waitlist control group who will receive the intervention at the end of the study, without interventionist support. The intervention (or kit) includes an introduction to the kit with a DVD, a binder including eight workbook modules offered in hard copy, and a CD with audio instructions to facilitate progressive muscle relaxation (PMR) training (included in module 8). An interventionist will meet with caregivers weekly for approximately 10-30 min. Caregivers will complete assessments at the start of the patient's RT (T1), at the conclusion of RT (T2), and 6-weeks post-RT (T3). All quantitative data will be in the form of self-report and qualitative data (intervention group only) will be collected via semi-structured interviews. All assessments will take place while at the RT clinic, by Redcap, by mail, or by phone.

Patient involvement. Patient participation is optional and only includes consent to abstract clinical information from his or her medical file or self-report this information. We will abstract clinical information from a patient's medical file if the patient is receiving radiation treatment at WFBMC. Patients who decide to receive radiation treatment outside of WFBMC may have incomplete clinical information in their WFBMC medical file. In these cases, patients will be asked to self-report any information collected in the Patient Clinical Information Form that is not available in their WFBMC medical file. Patient-reported and caregiver-reported clinical data forms will be abbreviated versions of the medical chart review collection form and only be collected at T1 to reduce participant burden. Further, it is unlikely that participants will be able to report on some of the clinical items we collect from the medical chart review. We will not collect self-report data from WFBMC patients during the proposed study. No patients will participate in the intervention.

## Subject Recruitment Methods

Participants will be recruited from the outpatient radiation clinics at the Comprehensive Cancer Center of Wake Forest University (CCCWFU) and the Lexington Medical Center, or by mail. Eligible patients will be identified through referral from the treating radiation oncologist and mailed a recruitment package for themselves and their primary informal caregiver (person providing the majority of unpaid care) before RT begins. For potential participants who have been identified before a clinic visit, the participants may be

contacted by a member of the study team to introduce the study and, if agreeable, the study team member will confirm with the patient that they will be present during their upcoming clinic visit to discuss the study and consent the participant(s). The study team will reach out to the patients' treatment team to inform them that they will approach the potential patient during their visit.
A study team member may also make contact with patient-caregiver dyads when presenting for the patient's simulation appointment, treatment consultation, or at the start of patient RT to determine willingness to participate. Potential participants who are identified during treatment consultation, but decide to receive treatment outside of WFBMC are still eligible to participate. If the primary informal caregiver is not present with the patient at the appointment, we will ask patients for permission to contact his or her caregiver by phone. A waiver of signed informed consent has been obtained in order to screen these participants (caregivers). At this time the study team member will confirm eligibility criteria with the participant. Study staff may check in caregiver medical records if accessible to confirm eligibility for the saliva portion of the study. Patient participation is optional, and only includes consent to abstract demographic and clinical information from his or her medical file. If the patient refuses to participate in the study, but the caregiver is still interested, he/she can still participate without patient consent. Caregivers will then be asked to report patient clinical information that is typically collected from the patient's medical record as part of the Patient Clinical Information Form. Caregivers will receive a $20 gift card at the completion of T1, T2and T3 assessments ($60 in gift cards total).
Caregivers who do not plan to attend visits in person may provide consent through a mailed informed consent form. The study team will contact the participant (caregiver) over the phone to review the Informed Consent Form. Any questions about the study will be answered so that the potential subject is fully aware of what the study entails. The study team member will mail or email the Informed Consent Form to the participant and the participant will be asked to print, sign, date and mail back the Informed Consent Form. Once the signed Informed Consent Form is received by the study team, the study member that consented the participant over the phone will print, sign and date the consent form. A copy of the completed Informed Consent Form will be mailed or emailed back to the participant. No study procedures will take place until both the participant and study team member sign and date the consent form.

**Inclusion/Exclusion Criteria.** Caregivers will be eligible if they are: (1) providing the majority of the informal (unpaid) care during RT for a patient meeting the below criteria, and (2) $\geq$18 years of age.

Caregivers will be excluded if they: (1) have a current cancer diagnosis, (2) cannot read/ communicate in English, (3) Caregivers who have an endocrine disorder (e.g., diabetes and thyroid disorders), or are currently taking a steroid-based medication are excluded from the saliva collection portion of this study.

Patient criteria: (1) have new or recurrent AJCC stage I-IV squamous cell carcinoma of the upper aerodigestive tract (including lip/oral cavity, nasopharnyx, salivary gland, oropharynx, hypopharynx, paranasal sinus, and larynx cancers), (2) have planned external beam radiotherapy (+/- chemotherapy) for 6-7 weeks, (3) $\geq$18 years of age, and (4) has an informal (unpaid) caregiver during RT. Patients will be excluded if they: (1) cannot read/ communicate in English.

**Sources of Materials**

**Sources of Research Material.** Data for this study will be collected from self-report surveys, qualitative interviews, participant self-collected salivary cortisol samples (for eligible caregivers only), and patient and caregiver medical chart review. Study investigators will have access to identifiable private information on participants, but it will be restricted to necessary data only. Data will be managed in a password protected data system for data entry and management. Access will be limited to study personnel.

**Use of Data.** Data will be restricted to research purposes only.

**HIPAA Guidelines.** Participant data will be protected through the use of ID numbers, in accordance with HIPAA guidelines. No individual data or participant identifiers will be reported, and this will be emphasized to participants.

**Informed Consent**

Study staff will obtain signed informed consent from each caregiver and care-recipient. Patient participation is optional, only includes consent to abstract treatment and disease-related information from his or her electronic health record or self-report this information for patients receiving treatment outside of WFBMC. A study investigator will explain the study and allow patients and caregivers to ask questions. We will carefully explain to patients that participation is restricted to collecting demographic and clinical information from their electronic health record and that participation will not impact their medical care.

**Potential Risks**

This study poses no more than minimal risks to participants. Caregivers may experience emotional discomfort when completing psychological instruments (coping with cancer self-efficacy, distress, burden, quality of life), but this is not expected to be greater than that encountered during routine psychological examination. Caregivers may potentially experience discomfort when completing workbook activities; however, the ultimate goal of these activities is to reduce negative psychological effects associated with providing care. The primary risk to all participants is loss of privacy and we will take appropriate steps (see confidentiality and privacy) to prevent this.

**Likelihood of Risks.** Risks associated with this study are unlikely.

**Minimizing Risks.** All study staff will be trained to interview in a sensitive manner. We will explain to participants that they do not have to complete any assessments that they do not wish to complete and that they may withdraw from participation at any time. Furthermore, caregivers' participation in the intervention is preference based, so they can opt out of modules. Caregiver psychological distress (anxiety and depression) data will be reviewed immediately and if levels are high, we will provide caregivers with contact information for the psychosocial oncology professionals at the cancer center. Dr. Weaver has training in clinical psychology and will assist with this process when necessary. All investigators will maintain current institutional protection of human subjects credentials.

**Confidentiality and Privacy**

Confidentiality will be protected by collecting only information needed to assess study outcomes, minimizing to the fullest extent possible the collection of any information that could directly identify subjects, and maintaining all study information in a secure manner. To help ensure subject privacy and confidentiality, only a unique study identifier will appear on the data collection form. Any collected patient/caregiver identifying information corresponding to the unique study identifier will be maintained on a linkage file, store separately from the data. The linkage file will be kept secure, with access limited to designated study personnel. Following data collection subject identifying information will be destroyed three years after closure of the study, consistent with data validation and study design, producing an anonymous analytical data set. Data access will be limited to study staff. Data and records will be kept locked and secured, with any computer data password protected. No reference to any individual participant will appear in reports, presentations, or publications that may arise from the study. Caregivers will be offered a private room away from the patient to complete surveys and will also have the option to complete surveys by phone with a study researcher. All interviews and sessions with the study interventionist will be completed away from the patient in a private room or by phone, if necessary. Use of study i-Pads does not need to occur in a private room; caregivers may choose to use the devices when patients are receiving treatment.

**Potential Benefits of the Proposed Research.** Caregivers may experience improvements in self-efficacy (in coping with cancer and abbreviated progressive muscle relaxation) psychological distress, burden, and QOL when participating in the intervention.

**Why Risks are Reasonable in Relation to Benefits.** The proposed intervention is highly unlikely to pose risks to participants. The minimal risk is outweighed by the potential benefits of the intervention for the caregiver.

**Data and Safety Monitoring**

The principal investigator will be responsible for the overall monitoring of the data and safety of study participants. The principal investigator will be assisted by other members of the study staff.

**Reporting of Unanticipated Problems, Adverse Events or Deviations**

All study staff will assist in monitoring safety of study participants. Safety events related to this research study are very unlikely to occur; however, any unanticipated problems or serious and unexpected adverse events (Grade 4 or Grade 5) will be promptly reported by the principal investigator or designated member of the research team to the IRB and the Safety and Toxicity Reporting Committee.

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**Appendices**

1. Study Schema
2. Recruitment letter
3. Study Flyer

4a. Patient Data Abstraction Form T1
4b. Patient Data Abstraction Form T3
5a. Caregiver surveys T1
5b. Caregiver surveys T2
5c. Caregiver surveys T3

6. Caregiver Saliva Collection Instructions
7. Semi-structured qualitative interview script for caregivers
8. Title Page for Workbook Binder

9a. Intervention workbook: Cancer Education
9b. Intervention workbook: Using your Resources
9c. Intervention workbook: Muscle Relaxation
9d. Intervention workbook: Social Support
9e. Intervention workbook: Positive Coping
9f. Intervention workbook: Healthy Behaviors
9g. Intervention workbook: Time Management
9h. Intervention workbook: Communicating with Others

10. Prepare to Care Kit Time Log
11. Weekly Needs Assessment
12. Intervention Procedure Manual
13. Introduction Video
14. Patient Decline Form
15. Caregiver Decline Form
16. Caregiver Withdrawal Form
17. Text Message Language