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Reducing Lung Cancer-Related Anxiety (RELAX)

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RELAX – SCHEMA

Pre-Screening

After completion of all three screening questionnaires, participant must score accordingly on at least one questionnaire to be eligible:

•score ≥8 on the anxiety subscale of the HADS [1] OR
•score ≥4 on the Distress Thermometer [92-94] OR
•score >5 on the 2-item screener from the Cancer Acceptance Scale [96]

↓

Designated staff person at each site to enter data in the screening log for all potential participants screened (necessary for the Primary Study Aim examining feasibility).

Randomization

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Stratification

75 participants will be stratified by baseline self-reported dyspnea and randomized to 3 groups 25 participants per Group:

Group A: The low-dose group will use the RESPeRATE device for 15 minutes once per day, at least 5 days per week for 12 weeks

Group B: The high-dose group will use the RESPeRATE device for 15-minute twice per day, at least 5 days per week for 12 weeks.

Group C: The usual breathing control group will use an identical control device (with nonrythmical tones that will not gradually slow down to reduce respiration rate) for 15 minutes once per day, at least 5 days per week over 12 weeks.

↓

Intervention

RESPeRATE device constantly synchronizes and automatically adjusts the melody/tones to the person's breathing pattern to reduce breaths per minute by prolonging exhalation. It is the size of a portable compact disc player with a respiration sensor. Throughout the intervention, participants rate symptom intensity before and after using the devices.

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Baseline Data Collection

Participants will be seen in clinic to receive their RESPeRATE device. The site coordinator will provide a demonstration on use of the device and assist participant with first use of the device. The following measures will be completed: Self-Reported Dyspnea, Spirometry (FEV1), Anxiety/Depression/Cancer-Related Worry, Fatigue, Cough Questionnaires, blood draw, and salivary cortisol collection.

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Weeks 1 – 11 Data Collection

Site coordinators will contact participants on a weekly basis by phone to assess use of the device, answer questions, and collect breathing data for the prior 7 days stored on the device.

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Week 6 (mid-intervention) Data Collection

In addition to the device breathing data, the following forms will be completed.by phone and/or mail. Brief questionnaires to include Self-Reported Dyspnea Anxiety/Depression/Cancer-Related Worry, Fatigue, and Cough Questionnaires.

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Week 12 Data Collection

Participants will be seen in the clinic for collection of final breathing data and to complete measures: Self-Reported Dyspnea, Spirometry (FEV1), Anxiety/Depression/Cancer-Related Worry, Fatigue, Cough Questionnaires, blood draw, and salivary cortisol collection. Participants will return their RESPeRATE device to the site coordinator.

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Endpoints

Feasibility (accrual, participation, adherence, retention), Anxiety, Cancer-Related Worry, Self-Reported Dyspnea, Spirometry (FEV1), Epigenetic and Gene Expression Changes, salivary cortisol changes (for those who are eligible related to Supplemental Objective 1.5)

Stratification: Site; Self-Reported Dyspnea
Study Sample: 75 participants (25 per group)
Study Duration: 12 weeks
Brief Eligibility Criteria:

- Past History of any lung cancer
- For Stage I-III disease, patients should be 2-24 months post-completion of surgery, radiation therapy and/or chemotherapy with no further planned treatment during the 12-week study and no evidence of disease.

  For Stage IV disease, patients may be receiving no treatment or may be receiving maintenance treatment with a target agent, chemotherapy, or immunotherapy provided the most recent imaging does not demonstrate progressive disease.
- After completion of all three screening questionnaires, participant must score accordingly on at least one questionnaire to be eligible:
  - score ≥8 on the anxiety subscale of the HADS [1] OR
  - score ≥4 on the Distress Thermometer [92–94] OR
  - score >5 on the Modified Cancer Acceptance Scale [96]
- Eastern Cooperative Oncology Group performance status 0-2

***Note:** Whole blood will be collected for DNA (for epigenetic analysis) and RNA (for gene expression analysis) isolation (at baseline and Week 12). These data will be used as preliminary data to indicate whether DNA methylation and/or gene expression variation correlates with changes in anxiety. This added genomics piece is a supplemental study objective and will capitalize on the larger parent RELAX trial. Twelve participants from each group will be required for analysis.

The Screening Log should be completed on all potential participants. It is located in CCRBIS. Once logged in to CCRBIS, go to information, select protocol and then screening log.

TABLE OF CONTENTS

1. OBJECTIVES

1.1. To assess feasibility (accrual, participation, adherence, retention) of a randomized study of device-guided breathing in 75 post-treatment lung cancer survivors with significant anxiety.

1.2. To obtain preliminary data on the variability and efficacy of two doses of a device-guided breathing intervention versus a usual breathing control group for reducing anxiety (primary outcome) and for improving self-reported cancer-related worry, dyspnea and respiratory functioning (secondary outcomes) in post-treatment lung cancer survivors.

1.3. To select the optimal dose of the device-guided breathing intervention (15 minutes once/day or twice/day) for subsequent randomized study.

1.4. Supplemental Objective: To determine if changes in anxiety attributed to device-guided breathing are correlated with epigenetic (DNA methylation) and/or gene expression changes.

1.5. Supplemental Objective: To obtain preliminary data on changes in salivary cortisol (diurnal slope, cortisol awakening response, area under the curve) in each intervention group and associations between salivary cortisol and anxiety.

2. BACKGROUND

2.1a Lung Cancer & Anxiety

Psychological concerns are among the most commonly reported unmet needs among post-treatment cancer survivors.[6] Psychosocial distress, including anxiety and depressive symptoms, is also common.[7,8] Up to 54% of post-treatment cancer survivors report clinically significant distress,[9,10] which is associated with multiple adverse outcomes, including decreased quality of life (QOL),[11–13] functional limitations,[14,15] poor sleep,[16,17] increased pain,[18] and even increased mortality.[19,20] The Institute of Medicine has emphasized post-treatment survivorship as a "distinct phase of cancer care," with a need for ensuring delivery of appropriate care for cancer survivors.[21] The need for interventions to reduce psychosocial morbidity in post-treatment cancer survivors is critical.[22,23] Psychosocial interventions for post-treatment cancer survivors may improve mental and physical health, potentially offsetting increased health care costs among distressed cancer survivors.[24]

The number of lung cancer patients with improved prognosis who could benefit from symptom management interventions is likely to increase substantially with improved screening methods, demonstrating a 20% reduction in mortality.[2] New clinical practice guidelines stemming from the National Lung Cancer Screening Trial (NLST) promoting lung cancer screening among high-risk groups[3,4] will likely increase lung cancer screening and result in more survivors with improved survival after earlier diagnosis. If clinical patterns reflect trial data, we expect 57% (versus 15% currently) of those diagnosed after screening to have localized disease.[2] An estimated 8.7 million adults in the U.S. will be eligible for low-dose computed tomography (LDCT) screening according to NLST eligibility criteria,[5] suggesting that the number of lung cancer patients will increase dramatically.

Anxiety is a significant problem for a substantial minority of lung cancer survivors. Anxiety symptoms are common in post-treatment cancer survivors,[6-10] significantly more so than pure depressive symptoms.[11] Compared with other cancer types, lung cancer patients have the highest rates of psychological distress[12] and report a higher number of unmet psychological needs, including fears of recurrence, physical disability or deterioration, difficulty making long-term plans, feeling dependent and helpless, and preoccupation with being ill.[13,14] Anxiety may

increase in the year after lung cancer surgery,[15] and recent studies have reported rates of clinically significant anxiety among lung cancer patients and post-treatment survivors ranging from 20-30%.[16-19]

Anxiety commonly co-occurs with distressing physical symptoms in patients with lung cancer.[18,20,21] The correlation between self-reported anxiety and dyspnea is estimated at 0.3.[21] This relationship is bidirectional, reflecting affective and physiological processes.[20,22-24] The number of lung cancer patients reporting dyspnea at some stage in their illness ranges from 55-90%.[20,21,25-27] Estimates of dyspnea in post-treatment ESLC survivors range from 40-60%.[28,29] Thus, dyspnea commonly occurs with anxiety after lung cancer treatment and is associated with worse functioning in multiple domains, greater distress, and lower quality of life.[22,23,30-33]

Breathing interventions have been effective at reducing anxiety/distress in cancer patients. Interventions focused on slow, deep breathing have decreased anxiety, stress symptoms, and physiological arousal in clinical populations and healthy adults.[34-37] Relaxation training is effective for relieving anxiety in cancer patients.[8,10] Breathing interventions have been incorporated into interventions to address dyspnea and related distress in lung cancer patients.[38] Few studies have examined concomitant changes in anxiety/distress, and anxiety level has not been a criterion for study entry. Such multi-component interventions have yielded promising results for anxiety and distress related to breathlessness in post-treatment lung cancer survivors.[39,40]

2.1b Background for Supplemental Objective: Epigenetic Changes & Anxiety

A number of recent studies have reported epigenetic changes associated with mental health and mood disorders. These have included post-traumatic stress disorder [81], depression [82], and suicide [83], and provide support for our hypothesis that epigenetic variation also contributes to changes in anxiety levels. Taken together, epigenetic variation in a number of individual genes and biological pathways has been identified for these conditions, and include inflammatory [82] and immune [81] related genes, as well as genes involved in the hypothalamic-pituitary-adrenal (HPA) axis. [84]

2.1c Background for Supplemental Objective: Cortisol Changes & Anxiety

Cortisol is a glucocorticoid and a biomarker of stress that is released from the hypothalamic pituitary adrenal (HPA) axis.[85, 87] 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, [86,87]post-traumatic stress disorder symptoms, [88] and anxiety. [89] Additionally, other similar psychosocial interventions have demonstrated changes in cortisol response. [90,91] Collectively, these studies support our hypothesis that changes in anxiety, attributed to the device-guided breathing, will be associated with changes in cortisol response.

Participants with endocrine disorders (e.g., diabetes and thyroid disorders) or on steroid-based medications are excluded from the cortisol portion of the study (with the exception of topical steroid creams/ointments which are permitted).

2.2 Study Intervention

The RESPeRATE device constantly synchronizes and automatically adjusts the melody/tones to the person's breathing pattern to reduce breaths per minute by prolonging exhalation. It is the size of a portable compact disc player with a respiration sensor (attached to an elastic belt worn over clothing) and a pair of headphones. The device is easy to use, and pilot participants have

found it appealing. In our pilot work and other studies, attrition rates have been low,[41] and adherence to the recommended rate of use has been high.[42-44]

For the low-dose group, participants will use the RESPeRATE device for 15 minutes once a day, at least 5 days a week for 12 weeks based on previous research that found this dose to be effective in reducing blood pressure.[45-47] For the high-dose group, participants will use the RESPeRATE machine in 15-minute increments twice a day, at least 5 days a week for 12 weeks, similar to the dose used in previous research conducted with other clinical populations with significant respiratory symptoms.[48,49] An effective rate of slow breathing is considered to be <10 respirations/minute.[42] The device automatically records use (i.e., accumulated duration, number of times used, average duration), initial breathing rate, and final breathing rate. This information will be used to measure intervention adherence.

2.3 Rationale for Intervention & Control Conditions

Device-guided breathing has not been studied in lung cancer survivors, yet it shows promising results in patients with chronic medical conditions and anxiety disorders. We propose use of a low-cost biofeedback device called RESPeRATE that can be used at home and guides patients to reduce their respiration rate and increase exhalation time. RESPeRATE has FDA approval as an adjunctive treatment for hypertension. Positive outcomes, including improved cardiorespiratory fitness and quality of life, have been observed in heart failure patients, particularly in groups receiving longer treatment and in participants who were successful at increasing their inhalation/exhalation ratio.[48,49] These studies did not assess anxiety or other psychological outcomes. A similar biofeedback device used in a single-arm pilot study for outpatients with anxiety disorders yielded significant reductions in anxiety and increased levels of relaxation,[50] suggesting that this approach is promising for reducing clinically significant anxiety symptoms.

Despite high rates of psychological distress, no behavioral interventions identified in a recent meta-analysis specifically targeted lung cancer survivors, and very few (8%) were conducted with any post-treatment survivors.[8,51] Research has identified the time after lung cancer treatment as particularly challenging, with reports of increased anxiety and uncertainty about the future.[52] Intervening with post-treatment lung cancer survivors with significant anxiety is important because psychological symptoms may receive less attention when contact with providers is less frequent. A recent review of psychosocial oncology interventions reported that only 5% of psychosocial oncology intervention studies addressed patients with significant distress,[51] even though high distress patients are most likely to benefit.[53]

The device-guided breathing intervention can be easily implemented at home with minimal instruction. This intervention could make behavioral treatments for anxiety more accessible to rural cancer survivors who experience mental health issues (including anxiety) at disproportionately higher rates than non-rural survivors [54,55] and often lack access to mental health professionals. [51,55-58] It could also be broadly applied in community-based cancer survivorship settings.

The proposed device-guided breathing intervention works by gradually slowing the respiration rate. Slow, deep breathing enhances parasympathetic tone, decreases acute and chronic sympathetic arousal, and reduces excitatory nervous activity, likely through cellular signaling activated by stretch receptors in the lungs.[59]

The relaxation response occurs acutely, but indicators of chronic sympathetic over-activation, such as resting hypertension, also decrease. Deep breathing improves respiratory and cardiovascular function, decreases effects of stress, and improves mental health.[1] Disordered

respiration is thought to be a key aspect of anxiety and stress-related disorders,[34,37] thus slow breathing also reduces anxiety and potentially dyspnea.[60,61]

Participants in the usual breathing control group will use an identical-looking device but only the RESPeRATE intervention is targeted at reducing respiration rate. The chimes for the control device will be nonrythmical tones that will not gradually slow down to reduce respiration rate. A similar control device is available from the same company and has been employed in other studies of the RESPeRATE device. [104]

3. SUMMARY OF STUDY PLAN

The RESPeRATE device constantly synchronizes and automatically adjusts the melody/tones to the person's breathing pattern to reduce breaths per minute by prolonging exhalation. It is the size of a portable compact disc player with a respiration sensor.

This pilot study will have three groups: RESPeRATE device-guided breathing group (low-dose) (n=25), RESPeRATE device-guided breathing group (high-dose) (n=25), and a usual breathing control group (n=25).

The low-dose group will use the RESPeRATE device for 15 minutes once per day, at least 5 days per week for 12 weeks.

The high-dose group will use the RESPeRATE device for 15-minutes twice per day, at least 5 days per week for 12 weeks.

The usual breathing control group will use an identical control device (with nonrythmical tones that will not gradually slow down to reduce respiration rate) for 15 minutes once per day, at least 5 days per week over 12 weeks.

After randomization, participants will be introduced to their assigned device and receive instructions and a demonstration on use. Participants will use the device at least 5 days per week for the assigned amount of time over 12 weeks.

All participants will complete pre- and post-intervention questionnaires spirometry (FEV1) at baseline and Week 12, weekly telephone contact to provide breathing data for the prior 7 days, brief mid-intervention questionnaires (at Week 6), and rate symptom intensity while using the devices (before and after one session each week). Eligible participants will collect salivary cortisol samples for three days following the baseline and Week 12 follow-up. Participants will have a blood draw at the baseline and Week 12 visits to determine if RNA and/or DNA methylation and/or gene expression variation correlates with anxiety changes. The duration of the study is 12 weeks.

Participants will be stratified by baseline self-reported dyspnea score and assigned with equal probability to either intervention group or the control group using variable length permuted block randomization. Block sizes will be chosen randomly to ensure that future assignments cannot be inferred from previous ones.

Drs. Danhauer and Weaver will meet with designated staff members from each NCORP site for a training session to review the protocol and provide intervention information. This training will take place at the annual meeting of the WF NCORP RB and/or at individual sites, as needed.

4. PARTICIPANT SELECTION

4.1. Inclusion Criteria

4.1.1 Past History of any lung cancer

4.1.2 For Stage I-III disease, patients should be 2-24 months post-completion of surgery, radiation therapy and/or chemotherapy with no further planned treatment during the 12-week study and no evidence of disease.

4.1.3 For Stage IV disease, patients may be receiving no treatment or may be receiving maintenance treatment with a target agent, chemotherapy, or immunotherapy provided the most recent imaging does not demonstrate progressive disease.

4.1.4 After completion of all three screening questionnaires, participant must score accordingly on at least one questionnaire to be eligible:

- Score ≥ 8 on the anxiety subscale of the HADS-Anxiety/Depression Scale[1] OR
- Score ≥ 4 on the Distress Thermometer[92–94] OR
- Score > 5 on the Modified Cancer Acceptance Scale [96]

4.1.5 Eastern Cooperative Oncology Group performance status 0-2

4.1.6 Willing/able to attend brief introductory session and use assigned device for the assigned period of time (15 minutes once or twice per day), at least 5 days per week for 12 weeks

4.1.7 Age ≥ 18 years

4.1.8 Must have telephone

4.2 Exclusion Criteria

4.2.1 Patient does not understand English

4.2.2 Active lung infection

4.2.3 Progressive cancer (must be considered no evidence of disease or stable)

4.2.4 Any change in psychotropic medications in past 30 days

4.2.5 Hearing loss that would preclude participating in interventions. Adequate hearing to participate will be determined via: (1) Response of “no” to the question [“Do you have a hearing problem now?”] Participants with hearing aids will be allowed to enroll as long as their hearing is adequate to hear the sounds on the study devices. If necessary, potential study participants will receive a brief test trial with the RESPeRATE device. If they indicate inability to hear the guiding tones, they will not be enrolled in the study.

Cortisol Exclusion

4.2.6. Participants with endocrine disorders (e.g., diabetes and thyroid disorders) or on steroid-based medications are excluded from the cortisol portion of the study (with the exception of topical hydrocortisone that is permitted).

4.3 Inclusion of Women and Minorities

Both men and women (as applicable) and members of all races and ethnic groups are eligible for this trial.

	Race/Ethnicity					
Gender	White, not of Hispanic Origin	Black, not of Hispanic Origin	Hispanic	Asian or Pacific Islander	Unknown	Total
Male	35	8	1	1	0	45
Female	25	4	1	0	0	30
Total	60	12	2	1	0	75

4.4 Recruitment and Retention Plan

We plan to recruit 75 lung cancer survivors through the WF NCORP RB. We anticipate that each participating site should be able to accrue one participant every 1-2 months for a total of 6-12 participants per site per year. Thus, with at least 12 study sites, we should finish accrual in approximately 12 months.

The WF NCORP RB sites will accrue to this trial. The WF NCORP RB has infrastructure in place to conduct the trial, including a web-based, interactive database for online participant registration and data management.

Potential participants may be recruited via (1) identifying lung cancer survivors through the site cancer registry; (2) in-clinic screening during medical appointments; (3) screening clinic charts; and (4) patient recruitment posters and recruitment letters.

Survivors will be approached in-person or by telephone by NCORP staff to ascertain interest and initial eligibility. We will track numbers of lung cancer survivors approached and screened, reasons for nonparticipation, and number randomized.

We have targeted a racial/ethnic minority recruitment goal per the table above (consistent with national rates of lung cancer). [76] To reach this goal we will use several strategies: (1) We will work directly with oncology nurse navigators at each site to ensure that our clinic referrals include eligible minority patients and to enlist assistance in recruiting these patients. Their trusted relationships with our lung cancer patients will lend credibility to our participation request and commitment to protect confidentiality; and (2) We will attempt to recruit all potentially eligible minority lung cancer survivors identified through institutional cancer registries, but whom we cannot recruit in person or via another medical center provider, by direct mail or phone. We will review our mailed recruitment materials to ensure that they are at an appropriate literacy level and are appealing to minority participants.

5. AGENT ADMINISTRATION

See Section 8. Protocol Specific Training Requirements

5.1 Adherence/Compliance

5.1.1 Adherence will be calculated as the actual amount of time the device is used divided by the prescribed time. Successful adherence will be defined as use of the device ≥75% of the time assigned. Note that all participants will be included in the primary analyses, regardless of adherence. A secondary analysis will include only those participants who were at least 75% adherent.

5.1.2 To determine intervention adherence, the RESPeRATE device tracks the number and duration of device uses and initial and final respiration rates.

6. DEVICE INFORMATION

6.1 Availability

The RESPeRATE devices are easily available and do not require any sort of prescription or permission to purchase.

6.2 Device Request and Distribution for Sites

Devices will be distributed to the sites from Wake Forest NCORP Research Base when the study is IRB approved at their site. Upon completion of the last participant, the site will return the RESPeRATE devices to the Wake Forest NCORP Research Base. See Section 6.6 for more information.

6.3 Device Accountability

Not applicable. The intervention is a simple and publicly available device. It is not a drug agent.

6.4 Registration/Randomization

6.4.1 Registration Process

An IRB letter of approval and an IRB approved consent form must be received by the Research Base Protocol Information Office – Attn: Site Coordinator prior to patient registration. Fax: (336) 716-6275

Fill out Appendix 2, Eligibility Checklist / Registration Form, and use this to complete the online registration.

Online Registration

NCORP site staff will register their study participants into the WF NCORP RB database by following the instructions below:

Log on to the WF NCORP Research Base registration web site at https://ccrbis.phs.wakehealth.edu. Enter your username and password (which may be obtained by contacting Robin Rosdhal RN OCN at rosdhal@wakehealth.edu). In the "Patient Registration and Protocol Information" table, click "Register Patient/Patient Info" with the corresponding protocol number found in the drop-down box to the right. Fill in the eligibility criteria forms using the drop-down boxes. If further information is needed by Data Management, they will contact you. Once the patient information has been entered online, print a copy of the eligibility checklist/registration form for your records. Press the submit button and a confirmation page will appear. Print this confirmation sheet for your records. The WF

NCORP Research Base Online Protocol Registration/Eligibility form, initial flow sheet, signed consent, histology reports, scan reports and lab reports (as required in protocol) should be faxed to (336) 713-6476 or mailed to Data Management:

Wake Forest School of Medicine
Department of Social Sciences and Health Policy
WF NCORP Research Base
Data Management Center
525 @ Vine, 4th Floor
P.O. Box 573152
Medical Center Boulevard
Winston-Salem, NC 27157-3152

These forms should be retained in the patient's study file. These forms will be evaluated during an institutional WF NCORP Research Base site member audit.

If you have questions related to the registration process or require assistance with registration, please contact the WF NCORP Research Base DMC between 8:30am and 4:00pm EST, Monday through Friday at (336) 713-3172 or 713-6507.

6.4.2 **Randomization Process**

Patients will be stratified by baseline dyspnea score (Cancer Dyspnea Scale score ≥ 8 v. < 8; see Table 7.8) and assigned with equal probability to either RESPeRATE intervention group or the control group using variable length permuted block randomization. Block sizes will be chosen randomly to ensure that future assignments cannot be inferred from previous ones. Patients need to report a minimum level of clinically significant anxiety symptoms (HADS-Anxiety/Depression Scale anxiety subscale ≥ 8), cancer-related worry (Modified Cancer Acceptance Scale score > 5), or distress (Distress Thermometer ≥ 4) to enter the study.

6.5 Unblinding Methods

Not applicable.

6.6 Device Return

Study participants will return any study devices to the site that issued them. All sites must return study devices to the Wake Forest NCORP Research Base at the following address:

Robin Rosdhal, RN, OCN
Wake Forest School of Medicine
Department of Social Sciences and Health Policy
NCORP Research Base – 525@Vine, 4th floor
P.O. Box 573152
Medical Center Boulevard
Winston-Salem, NC 27157

7. CLINICAL EVALUATIONS AND PROCEDURES

7.1 Schedule of Events

Participants will be randomized to one of three groups: RESPeRATE device-guided breathing group (low-dose) (n=25), RESPeRATE device-guided breathing group (high-dose) (n=25), and a usual breathing control group (n=25).

The low-dose group will use the RESPeRATE device for 15 minutes once a day, at least 5 days per week for 12 weeks.

The high-dose group will use the RESPeRATE device for 15-minutes twice a day, at least 5 days per week for 12 weeks.

The usual breathing control group will use an identical control device (with nonrythmical tones that will not gradually slow down to reduce respiration rate) for 15 minutes once per day, at least 5 days per week over 12 weeks.

After randomization, participants will be introduced to their assigned device and receive instructions and a demonstration on use. Participants will use it at least 5 days per week for the assigned amount of time over 12 weeks. All participants will complete pre- and post-intervention questionnaires, spirometry (FEV1) at baseline and Week 12, weekly telephone contact to provide breathing data for the prior 7 days, brief mid-intervention questionnaires by mail with a stamped return envelope enclosed and/or telephone contact at Week 6, and rate symptom intensity while using the devices (before and after one session per week). Eligible participants will collect salivary cortisol samples for three days following baseline and the Week 12 follow-up. Participants with endocrine disorders (e.g., diabetes and thyroid disorders) or on steroid-based medications (topical steroid medications are permitted) are excluded from the cortisol portion of the study. Participants will have a blood draw at the baseline and 12 week visits, to determine if RNA and/or DNA methylation and/or gene expression variation correlates with anxiety changes. The duration of the study is 12 weeks.

The NCORP staff member will instruct each participant in use of the RESPeRATE device at baseline. Participants will be told that RESPeRATE analyzes a person's breathing pattern and plays 2 distinct tones that guide the person to inhale and exhale. The RESPeRATE control device looks and sounds identical but is not programmed to gradually slow breathing rate as in the active intervention arm. All participants will be provided with written instructions for the assigned device and will be observed using the device during the visit. To enhance adherence, we will have a NCORP staff member call participants weekly to assess experience with the device, troubleshoot difficulties that may have arisen and obtain breathing data for the prior 7 days. Participants who have not been using the device at the recommended frequency will troubleshoot ways of overcoming barriers to adherence as needed.

Self-reported dyspnea and spirometry (FEV1) include questionnaires and a pulmonary function test (PFT). These measures will be administered in-person at the NCORP site during baseline and post-intervention (Week 12) assessments. A shorter battery will be administered mid-intervention via mailed paper questionnaire with a stamped return envelope enclosed (Week 6). Any serious adverse event grade 4 or 5 related to the intervention will be reported to the WF NCORP RB at the time they become known to the NCORP site. (See Section 10.0)

7.2 Pre-Screening Evaluation/ Baseline Testing

Pre-Screening:

A minimal score on one of three measures is required for study eligibility. These measures include: (1) Score > 5 on the Modified Cancer Acceptance Scale (two-item screener) OR (2)

Score ≥ 4 on the Distress Thermometer OR (3) Score of ≥ 8 on the anxiety subscale of the HADS-Anxiety/Depression Scale.

- The single-item Distress Thermometer is a brief, single-item screening tool assessing distress from 0 (no distress) to 10 extreme distress). Recent meta-analyses have identified a score ≥ 4 as an appropriate cut-off for identifying significant levels of distress.
- The Modified Cancer Acceptance Scale assesses fear of disease recurrence and consists of 2 items: ‘‘I worry about the cancer returning’’ and ‘‘I am anxious about my health.’’ Both items are rated on a 4-point Likert scale ranging from ‘‘does not apply to me at all’’ to ‘‘completely applies to me.’’ Scores range from 2 to 8.
- The full HADS (including the depression subscale) will be administered either over the phone or in person. Scores will be used as the baseline value to minimize burden by administering the measure again within a short time interval. The HADS-Anxiety/Depression Scale is a 14-item self-report measure that is scored by assigning a numeric value to each of the 14 items (0, 1, 2, or 3), and then totaling item scores. The minimum score is 0 and the maximum score is 42. Anxiety and depression subscales each consist of the sum of 7 questions (range 0-21 for each subscale). A score $\geq$ 8 on the anxiety subscale indicates significant anxiety. Some items may be left blank. In this case, scores will be calculated as long as more than half the items are answered. The scores will be calculated as the mean of the responses times the number of items in the scale (7 for the subscales and 14 for the overall scale).
- Eastern Cooperative Oncology Group performance status 0-2.

Baseline testing:

- Hospital Anxiety/Depression Scale (HADS) (use form completed for screening)
- Cancer Worry Scale
- Cancer Dyspnea Scale (CDS) **will be needed for registration**
- PROMIS Fatigue
- Manchester Cough in Lung Cancer Scale
- Activities form
- Current medications
- Participant expectations rating
- Spirometry (forced expiratory volume in one second [FEV1])
- Visual Analogue Scales (VAS) for distress, anxiety and dyspnea—this form should be completedonce a week before and after a single use of the device during Weeks 1-12
- Blood draw—a blood sample of approximately 2 teaspoons will be taken from a vein in the arm/central line for DNA methylation levels and RNA.
- Salivary cortisol collection—saliva samples will be collected by participants at time of awakening, 30 minutes post-awakening, and at bedtime for three consecutive days (9 samples per participant).

7.3 Evaluations during Study Intervention at Weeks 1 - 11

Weeks 1 - 11:

- Weekly Check-in Call/Data Capture from Device via telephone interview. The participant will be contacted by phone to assess his/her experience with the device and troubleshoot difficulties that may have arisen and obtain breathing data for the prior 7 days. The participant will also be asked if (s)he completed the once weekly

VAS for distress, anxiety, and dyspnea (before and after a single use of the device each week). If (s)he has not done so, (s)he will be asked to complete the VAS form before and after their next use of the device. Participants who have not been using the device at the recommended frequency will troubleshoot ways of overcoming barriers to adherence, as needed.

Week 6:

- In addition to phone contact, participants are to complete the following questionnaires (may be done via mail):
- Hospital Anxiety/Depression Scale (HADS)
- Cancer Worry Scale
- Cancer Dyspnea Scale
- PROMIS Fatigue
- Manchester Cough in Lung Cancer Scale
- Activities form
- Weekly Check-in Call/Data Capture from Device Form (via telephone)

7.4 Evaluations at Completion of Study Intervention

Week 12:

- Hospital Anxiety/Depression Scale (HADS)
- Cancer Worry Scale
- Cancer Dyspnea Scale (CDS)
- PROMIS Fatigue
- Manchester Cough in Lung Cancer Scale
- Activities form
- Current medications
- Collect Weekly Check-In Call/Data Capture from Device forms
- Intervention feedback
- Spirometry (forced expiratory volume in one second [FEV1])
- Visual Analogue Scales (VAS) for distress anxiety and dyspnea
- Blood draw—a blood sample of approximately 2 teaspoons will be taken from a vein in the arm/central line for DNA methylation levels and RNA.
- Salivary cortisol collection, if applicable—saliva samples will be collected by participants at awakening, 30 minutes post-awakening, and at bedtime for three consecutive days (9 samples per participant)

7.5 Methods for blood draw and transport

7.5.1 For detection of DNA methylation levels:

Genomic DNA will be isolated from whole blood (one 8/8.5 ml yellow-top, ACD tube). DNA will be isolated using the AutoPure LS (Qiagen, Inc.), and then bisulfite-converted using the EZ DNA Methylation Gold kit (Zymo, Irvine, CA). To determine the proportion of DNA methylation at each of over 485,000 CpG sites, we will use the HumanMethylation450 BeadChip (Illumina, Inc.) along with the iScan Reader (Illumina, Inc.).

7.5.2. RNA:

RNA will be isolated from whole blood collected in one 2.5/4 ml tube using the PAXgene Blood RNA System (Qiagen), following the manufacturer's instructions. The PAXgene system stabilizes the RNA and minimizes degradation, a process that can lead to false results in

subsequent analysis. As with the DNA, the whole blood for RNA will be stored with the tube upright at room temperature until transported to the laboratory. RNA will be isolated with the PAXgene Blood RNA System (Qiagen), following the manufacturer's instructions. Once isolated, RNA will be evaluated for quality and quantity using the RNA 6000 Nano chips and analyzed on the Agilent 2100 Bioanalyzer (Agilent Techonology, Inc). Expression profiles will be generated with HumanHT-12 v4 Expression BeadChips (Illumina, Inc.), which assay over 47,000 probes spanning approximately 30,000 genes. BeadChips will be scanned with the iScan Reader (Illumina, Inc.), and preliminary analysis will be performed with Genome Studio (Illumina, Inc.).

Blood samples will be collected at baseline and Week 12. Once collected, Dr. Timothy Howard's lab will be notified by phone at (336) 713-7509. Samples will be processed and shipped per instructions in Appendix 19.

7.5.3. Methods for cortisol collection, assays, and mailing:

Participants with endocrine disorders (e.g., diabetes and thyroid disorders) or on steroid-based medications (topical steroid medications are permitted) are excluded from the cortisol portion of the study.

Materials for saliva collection will be distributed to participants at baseline. Materials can be provided in-person at the clinic visit or the materials can be shipped to the participant's home. Participants will collect saliva samples three times a day (at awakening, 30 minutes post-awakening, and bedtime) for three consecutive days following baseline and three consecutive days following the Week 12 follow-up visit. 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 nine samples have been collected at each time point (baseline, Week 12 follow-up), participants may return their samples and saliva collection diaries by: 1) returning them to the local clinic within 2 weeks of collection and the local clinic will take responsibility for sending them to Wake Forest NCORP Research Base, or 2) using pre-paid postage to return their samples and saliva collection diaries directly to the Wake Forest NCORP Research Base. Once received at the Wake Forest NCORP Research Base, all samples will be refrigerated (-80° C) until assayed.

Samples will be assayed in duplicate at Wake Forest NCORP Research Base using The Salimetrics® Cortisol Enzyme Immunoassay Kit (State College, PA). At no time in the testing process are samples identified by name of subject or any information that would link the sample directly to an individual. 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 60 days and then disposed of per applicable waste handling regulations.

7.6 Post-intervention Follow-up Period – N/A

	Pre-Screen	Screen	Baseline	Week 1	Week 6	Week 12

7.7 Methods for Clinical Procedures – N/A

7.8 Study Parameter Table

Consent		X				
Flow Sheet			X		X	X
Screening Form (A) (To be completed on eligible and ineligible patients that do not want to participate)		X				
HADS-Anxiety/Depression Scale [64-66, 68-70] (pre-screen if done by phone in advance OR at baseline if done in person).	X (C)				X	X
Distress Thermometer (1 item)	X					
Modified Cancer Acceptance Scale (2 items)	X					
Cancer Worry Scale (8 items) [95]			X		X	X
Spirometry (FEV1)			X			X
Cancer Dyspnea Scale (CDS) [62, 63, 67, 73] Will be needed for registration			X (D)		X	X
PROMIS Fatigue [79]			X		X	X
Manchester Cough in Lung Cancer Scale [80]			X		X	X
Activities Form			X		X	X
Current Medications			X			X
Weekly Check-In Call/Data Capture from Device (via telephone interview)			X	Weekly (1-12)		
Participant Expectations [74, 75]			X			
Intervention Feedback					X	
Early Withdrawal Form		If patient withdraws prior to completion of study.				
RNA/DNA Labs			X			X
Salivary cortisol collection (B)			X			X
** Visual Analogue Scales for Distress, Anxiety, and Dyspnea [71, 72]		Should be requested by mail and submitted at Week 6 and at completion of the Week 12 study. Completed before and after a single use of the device each week during Weeks 1-12. (Participant will need several double sided forms) 1 selected use/week x 12 weeks = 12 forms				

(A) Designated staff person at each site will log-in to CCRBIS to enter data in the screening log for all potential participants screened (necessary for the Primary Study Aim examining feasibility).

(B) *Participants with endocrine disorders (e.g., diabetes and thyroid disorders) or on steroid-based medications are excluded from the salivary cortisol portion of the study. Topical steroid medications (creams/ointments) are permitted
(C) Pre-screen HADS may be used for baseline and does not need to be repeated.
(D) CDS will need to be collected prior to registration

7.9 Off Treatment Criteria

Participants may stop using the device for the following reasons: completed the protocol-prescribed intervention, adverse event or serious adverse event, inadequate device functioning, noncompliance, or medical contraindication.

Participants will continue to be followed, if possible, for safety reasons and in order to collect endpoint data according to the schedule of events. Participants will not be replaced for discontinuing the device.

7.10 Off Study Criteria

Participants may go "off-study" for the following reasons: the protocol intervention and any protocol-required follow-up period is completed, adverse event/serious adverse event, lost to follow-up, non-compliance, concomitant medication, medical contraindication, withdraw consent, or death.

We anticipate an approximate 20% attrition rate, and the total sample size has been adjusted accordingly.

8. PROTOCOL SPECIFIC TRAINING REQUIREMENTS

8.1 Specific Training Procedures or Certification Procedure

Several methods will be used in training sites. A training session will be held at the annual Research Base meeting and/or other meetings as designated by Drs. Danhauer and Weaver.

9. SPECIMEN MANAGEMENT

9.1 Blood for Research Testing

Blood samples will be shipped and stored with a unique identifier and will not include any information protected by HIPAA regulations. Storage for blood samples is located at Wake Forest University Baptist Medical Center.

Center for Genomics & Personalized Medicine Research
Wake Forest School of Medicine
NRC Bldg., Room 319
Medical Center Blvd.
Winston-Salem, NC 27157
Phone: (336) 713-7509

(See Appendix 18 and 19 for further lab instructions.)

After study-related tests have been performed, blood samples/blood derivatives (serum, plasma, PBMCs and their derivatives) are returned to the freezer. Samples will be stored for up to 60 days to allow assay data to be reviewed by the supervisor and samples needing to be

retested identified. Samples needing retesting are again thawed, analyzed and refrozen. After assays are complete, samples will be disposed of per applicable waste handling regulations.

10 REPORTABLE ADVERSE EVENTS/SERIOUS ADVERSE EVENTS

Only report **unexpected serious adverse events,** Grades 4 and 5, which are related to the use of the breathing device used in this study.

Adverse Event/Serious Adverse Event reporting begins after the informed consent is signed. Serious Adverse Events occurring within 30 days of study completion must be reported via FDA Form 3500 (MedWatch).

11. STUDY MONITORING

11.1 Data Management Schedule

The Eligibility checklist/Registration Form should be completed on-line prior to placing the patient on study. Data forms will be submitted to the WF NCORP Research Base. See Section 6.4.1 for mailing address, or fax to (336) 713-6476.

Form	Submission Schedule
HADS Form	Within 14 days of Pre-Screen or Baseline, Week 6, Week 12
Distress Thermometer	Within 14 days of Pre-Screen
Modified Cancer Acceptance Scale	Within 14 days of Pre-Screen
Cancer Worry Scale	Within 14 days of Baseline, Week 6, Week 12
Informed Consent	Within 14 days of Baseline
Cancer Dyspnea Scale (CDS)	Within 14 days of Baseline, Week 6, Week 12
Flow Sheet/Addenda	Within 14 days of Baseline, Week 6, Week 12
Current Medications	Within 14 days of Baseline, Week 12
Participant Expectations	Within 14 days of Baseline
PROMIS Fatigue	Within 14 days of Baseline, Week 6, Week 12
Manchester Cough in Lung Cancer Scale	Within 14 days of Baseline, Week 6, Week 12
Activities Form	Within 14 days of Baseline, Week 6, Week 12
Weekly Check-In/Call Data Capture from Device	Within 14 days of Week 6, Week 12
Visual Analog Scales	Within 14 days of Week 6, Week 12
RNA/DNA Lab Sample Form	Within 14 days of Baseline, Week 12
Intervention Feedback	Within 14 days of Week 12
Early Withdrawal Form	Within 14 days of Upon withdrawal from active treatment or consent
Screening Form (Eligible and Ineligible participants) **	Monthly

**** Designated staff person at each site will log-in to CCRBIS to enter data in the screening log for all potential participants screened (necessary for the Primary Study Aim examining feasibility).**

11.2 Case Report Forms

Participant data will be collected using protocol-specific case report forms (CRF).

11.3 Source Documents

Source documents are the original signed and dated records of participant information (e.g., the medical record, shadow chart) which may include electronic documents containing all the information related to a participant's protocol participation. Source documents are used to verify the integrity of the study data, to verify participant eligibility, and to verify that mandatory protocol procedures were followed. An investigator and other designated staff are required to prepare and maintain adequate and accurate documentation that records all observations and other data pertinent to the investigation for each individual participating in the study. All data recorded in the research record (including data recorded on CRFs) must originate in the participant's medical record, study record, or other official document sources.

Source documents substantiate CRF information. All participant case records (e.g., flow sheets, clinical records, physician notes, correspondence) must adhere to the following standards:

- Clearly labeled in accordance with HIPAA practices so that they can be associated with a particular participant or PID;
- Legibly written in ink;
- Signed and dated in a real time basis by health care practitioner evaluating or treating the participant; and
- Correction liquid or tape must not be used in source documents or on CRFs. Corrections are made by drawing a single line through the error. Do not obliterate the original entry. Insert the correct information, initial, and date the entry.

All laboratory reports, pathology reports, x-rays, imaging study and scans must have:

- Complete identifying information (name and address of the organization performing, analyzing, and/or reporting the results of the test); and
- Range of normal values for each result listed.

11.4 Data and Safety Monitoring Board

The Data Safety Monitoring Board meets every six months to review all phase II and phase III protocols. The Board includes members demonstrating experience and expertise in oncology, biological sciences and ethics. The DSMB report is generated by the statistician and includes a summary of accrual, adherence, and retention, descriptive statistics for baseline characteristics and patient status, descriptions of all adverse events and toxicities, estimates of data completeness, a summary of the primary and secondary outcome measures.

11.5 Record Retention

Clinical records for all participants, including CRFs, all source documentation (containing evidence to study eligibility, history and physical findings, laboratory data, results of consultations, etc.), as well as IRB records and other regulatory documentation will be retained by the Investigator in a secure storage facility in compliance with HIPAA, OHRP, FDA regulations and guidance, and NCI/DCP requirements unless the standard at the site is more stringent.

Record retention should be 5 years after the study is discontinued for studies without an IND (21 CFR 312.62).

11.6 CDUS Reporting

The Wake Forest NCORP Research Base Data Management Center will submit quarterly reports to DCP/CTEP by electronic means using the Clinical Data Update System (CDUS).

12. STATISTICAL CONSIDERATIONS

12.1 Study Design/Endpoints

Objectives: The objectives of this pilot study are:

1) To evaluate the feasibility of conducting a randomized phase III study to test the efficacy of device-guided breathing in post-treatment lung cancer survivors with significant anxiety. Feasibility will be assessed using measures of accrual, participation, adherence, and retention.

2) To collect preliminary data on the variability and efficacy of two doses of a device-guided breathing intervention versus a usual breathing control group for reducing anxiety (primary outcome) and for improving self-reported cancer-related worry dyspnea, and respiratory functioning (secondary outcomes) in post-treatment lung cancer survivors.

3) To select the optimal dose of the device-guided breathing intervention (15 minutes once/day or twice/day) for a subsequent randomized study. The optimal dose will be defined as the one that results in the greatest improvement in anxiety scores at 12 weeks.

A parallel, randomized pilot study will be conducted to address these objectives. Eligible patients will be stratified initial dyspnea level and randomized with equal probability to high dose device-guided breathing, low-dose device-guided breathing, or a usual breathing control. Study endpoints include anxiety (primary outcome: anxiety subscale of the HADS-Anxiety/Depression Scale), dyspnea, and respiratory function. These constructs will be measured at baseline and 6 and 12 weeks post-randomization. Estimates of treatment efficacy will be obtained using the "intent to treat" approach. That is, all randomized patients will be included in the primary analyses whether or not they were treated according to protocol.

4) Supplemental Objective: To determine if changes in anxiety attributed to device-guided breathing are correlated with epigenetic (DNA methylation) and/or gene expression changes.

5) Supplemental Objective: To obtain preliminary data on changes in salivary cortisol (diurnal slope, cortisol awakening response, area under the curve) in each intervention group and associations between salivary cortisol and anxiety.

12.2 Sample Size/Accrual Rate

The sample size for this trial will be based on statistical selection theory criterion as described by Simon et al.[77] For a selection trial, one simply chooses the regimen that results in the "best" response. While Simon used this idea in the context of choosing the regimen with the best tumor response, the idea is applicable to outcomes with other distributions (in addition to the binomial). In our trial, the response is self-reported anxiety, which we will assume is normally distributed, so the best regimen will be the one with the lowest mean anxiety score. We will proceed to a phase III trial if one of the RESPeRATE intervention arms results in the least anxiety, and the mean anxiety score in that group is at least 0.5 standard deviations (SD) less than mean anxiety score in the control group. The sample size is chosen to ensure a high probability of selecting the best arm, assuming that the mean anxiety score in the low dose arm is 0.5 SD less than the mean in the control group and the mean anxiety score in the high dose arm is 1.0 SD less than the mean in the control arm. Under these assumptions, we used

simulations to determine the sample size needed in each group to ensure that the probability of selecting the best regimen was 90%. We randomly selected n independent observations from the normal distribution with an SD = 1, calculated the mean anxiety scores for each group, and selected the group with the least observed mean. This was repeated 200,000 times. The probability that the best regimen was chosen is calculated as the proportion of times (of the 200,000 repetitions) that the group with the true lowest mean was selected. In addition to selecting the best regimen, we will only pursue a subsequent phase III trial if there is some evidence of effect. Thus, we will require that the mean in the best regimen is at least 0.5 SD lower than the mean for the control group. Using simulations, we find that 20 patients per group provides 90% probability that the best regimen will be chosen and the mean in that group be at least 0.5 SD lower than the mean in the control arm. Assuming a 20% dropout, we will accrue a total of 75 participants to this study (20x3/.8). Assuming no effect of the RESPeRATE device, we have 90% probability of stopping with the phase II trial.

12.3 Randomization and Stratification

Patients will be stratified by baseline dyspnea (0-7 versus 8+ for CDS total score) and assigned with equal probability to either RESPeRATE group or the control group using variable length permuted block randomization. Block sizes will be chosen randomly to ensure that future assignments cannot easily be inferred from previous ones. There will be no interim analyses for this pilot study, and analyses will not be done separately for each stratum.

12.4 Primary Endpoint(s)

The primary objective of this study is to collect data that will allow us to assess the feasibility of conducting a phase III randomized study of device-guided breathing in lung cancer survivors with significant anxiety. These endpoints include: participation, accrual, adherence, and retention.

The participation rate will be calculated as the proportion of eligible patients who agree to participate.

The accrual rate will be calculated as the number of patients accrued to the study divided by the number of months of accrual.

The actual amount of time the participant used the device will be retrieved from each device. Adherence will be calculated as the actual amount of time the device is used divided by the prescribed time. Successful adherence will be defined as use of the device ≥75% of the time assigned. We will also estimate the proportion of patients who use the device more than prescribed. (If “low-dose” participants use the device more than prescribed, this may limit our ability to detect a dose effect.)

Retention will be calculated as the number of participants who complete the final assessment divided by number randomized.

Confidence intervals for the binomial proportions will be calculated using methods described by Wilson.[78] Approximate 95% confidence intervals based on the normal distribution will be calculated for the continuous measures.

The clinical endpoints are anxiety (primary outcome: anxiety subscale of the HADS-Anxiety/Depression Scale), cancer-related worry, dyspnea, and pulmonary function at baseline and 6 and 12 weeks post-randomization. Estimates of treatment efficacy will be obtained using the “intent to treat” approach. Descriptive statistics (means, standard deviations, frequencies,

etc.) will be presented for each outcome measure at baseline and follow-up points stratified by treatment arm. Repeated measures (RM) ANCOVA models (fitted using PROC MIXED in SAS) will estimate the treatment effect for each outcome, test for treatment differences, and obtain adjusted post-treatment estimates of the variability of these outcomes. Estimates of outcome measure variability will be used to determine sample size for the subsequent trial. The primary RM ANCOVA model will include time, treatment arm, and the stratification factors. An unstructured covariance matrix will be used to account for the within-patient correlation over time. In secondary models, additional covariance structures (Toeplitz, Autoregressive, Compound Symmetry) will be assessed and the optimal structure will be chosen based on likelihood ratio tests for nested structures and the BIC statistic for non-nested structures. Least squares means and 95% confidence intervals will be provided for each outcome, stratified by treatment arm, and for the difference between treatment arms. Regression diagnostics and residual plots will be used to find appropriate transformations for variables in the model.

Subsequent RM ANCOVA models will include additional covariates (e.g., age, sex, stage) to correct for chance imbalances in important prognostic variables and account for variability in outcome measures due to covariates. These latter models will inform us of possible stratification factors for the subsequent trial. Limited exploratory analyses will be done to determine if the treatment effect differs for different levels of covariates (e.g., by including treatment by covariate interactions in the model) to see if the subsequent trial should be done in particular subsets of lung cancer survivors. It is likely that some data will be missing. In addition to the mixed models above, we will use multiple imputation pattern-mixture models under various assumptions (e.g., participants in the active arms who drop out would have subsequent patterns similar to participants in the control arm) to assess the sensitivity of our modeling assumptions.

The optimal dose will be defined as the one that results in the greatest improvement in anxiety scores at 12 weeks (based on estimates from the RM ANCOVA model). This dose will be used in the subsequent trial, assuming that it is one of the RESPeRATE intervention groups.

Assuming the 95% confidence interval for the treatment effect includes a clinically meaningful difference, the sample size for the subsequent phase III trial will be determined based on detecting a clinically meaningful difference with a high power using estimates of variability obtained in this study. The estimates of retention and adherence observed in this study will be used to refine that sample size estimate. Subsequent trial feasibility will be assessed based on our ability to recruit the required number of participants. For that, we will use the accrual and participation rates observed in the participating sites. For sites that did not participate in this pilot study, accrual will be estimated by multiplying the estimated number of eligible patients times the participation rate across the participating sites.

12.5 Secondary Endpoint(s)

Epigenetic and Gene Expression Analyses.
To characterize the DNA methylation and gene expression patterns between the different groups, mixed effects models will be used. Changes of methylation or expression levels will be treated as the dependent variables and the intervention groups will be the independent variable of interest. Baseline methylation or expression levels, age, chip, chip position, and other covariates will be adjusted in the model. After comparing the fit of these data at a set of 20 random CpG markers (for the methylation analysis only), the alternative paired difference between baseline and twelve weeks (percent change dividing the difference by baseline value) will be examined to see if it provides a better fit to these data.

To determine if changes in anxiety are associated with methylation or gene expression patterns, mixed effects models will be used, and changes in anxiety variables will be treated as the dependent variables. Baseline methylation or expression, change of methylation or expression,

intervention group, and interaction between intervention group and change of methylation or expression will be included in the model, along with the appropriate covariates. If the interaction effect is significant, it means that the association between the change in anxiety and change in methylation or expression proportion is not the same between the two exposure groups. Multiple comparisons will be adjusted using Bonferroni correction as before.

Salivary Cortisol Analyses. Participants with endocrine disorders (e.g., diabetes and thyroid disorders) or on steroid-based medications are excluded from the cortisol portion of the study (topical hydrocortisone cream permitted). Cortisol levels will be assessed upon awakening, 30 minutes post-awakening, and at bedtime for three consecutive days at baseline and three consecutive days at 12 weeks. Several 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), and the diurnal slope (change in cortisol between awakening and bedtime). Scatterplots and correlations will be used to quantitate the associations between these measures, and anxiety at each time (baseline and 12 weeks) as well as association between the change in cortisol measures and the change in anxiety. Additionally, mixed effects models, as described above, will be used to assess the association between baseline cortisol and changes in anxiety over time. To assess group differences in cortisol parameters, each of these measures at 12 weeks will be used as dependent variables in analysis of covariance models, using appropriate transformations as needed. Baseline levels of the measures will be used as covariates along with treatment group.

12.6 Reporting and Exclusions

An objective of this study is to estimate adherence and retention as defined above in Section 12.4. Note that all participants will be included in all primary analyses, regardless of adherence or retention using all data that have been collected. Secondary analyses will be conducted using those participants who were at least 75% adherent to see if the “per protocol analysis” gives similar results as the “intent-to-treat analysis.”

12.7 Evaluation of Toxicity

All participants will be evaluable for serious adverse events from the time of their randomization. Toxicities will be evaluated using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Fisher exact tests will be used to assess differences in toxicity rates between the three arms.

12.8 Evaluation of Response

Tumor response is not an outcome. Response for this study will be the change in anxiety from baseline to 12 weeks, and this outcome will be assessed in all participants. Analysis of this outcome is described above in Section 12.4.

12.9 Interim Analysis

There will be no formal stopping rules based on interim analyses for this pilot study. However, all Research Base studies are reviewed by the DSMB every six months so the data from this study will be reviewed on that schedule. The report completed for the DSMB includes a summary of accrual, adherence, and retention, descriptive statistics for baseline characteristics and patient status, descriptions of all adverse events and toxicities, estimates of data completeness, a summary of the primary and secondary outcome measures.

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