CCCWFU 01716: PROGRAMS TO SUPPORT YOU DURING CHEMOTHERAPY (PRO-YOU)

A randomized controlled pilot study of yoga compared to an attention control in patients receiving chemotherapy

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Tool Revision History

Version Number: 2
Version Date: June 11, 2015
Summary of Revisions Made:

- Added the ability to train additional back-up interventionists and have phlebotomists conduct blood draws
- Edited the description regarding timing of data abstracted during chart reviews to be consistent across sections of the protocol
- Changed wording to clarify that the study staff holding randomization would not be the same as those collecting data
- Clarified wording regarding adverse events to state that only AEs related to the study intervention or measures will be captured.

Version Number: 3
Version Date: December 7, 2015
Summary of Revisions Made:

- Modified language for clarification in the description of the active intervention.
- Modified footer in Schedule of Evaluations to match the data safety and monitoring plan regarding identification of adverse events.
- Modified timeframe from one to two weeks in the plan for handling any modifications to the standard schedule.
- Allows for participant preference in the time daily surveys are sent and the ability for a study team member to contact participants to facilitate completion of daily surveys.

Version Number: 4
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Summary of Revisions Made:

- Adapted wording to be specific to procedures at new recruitment site, the Comprehensive Cancer Center of Wake Forest University
- Changed personnel to be relevant for the new recruitment site

Version Number: 5
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Summary of Revisions Made:

- Changed Co-Investigator Dr. Alistar to Dr. Desnoyers because of her relocation

Version Number: 6
Version Date: March 1, 2019
Summary of Revisions Made:

- Changed Co-Investigator Dr. Desnoyers to Dr. Rocha Lima because of his relocation
- Changed eligibility criteria and relevant justification

Version Number: 7
Version Date: July 15, 2019
Summary of Revisions Made:

- Updated power analyses to be based upon determining an estimate of the variance.

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PRÉCIS

Study Title

Programs to Support You During Chemotherapy (Pro-You): A randomized controlled pilot study of yoga compared to an attention control in patients receiving chemotherapy

Objectives

Aim 1: To conduct a pilot randomized controlled trial of a Yoga Skills Training (YST) versus an Attention Control (AC) group among adults with a gastrointestinal (GI) cancer receiving chemotherapy to determine preliminary efficacy for the primary outcome of fatigue, secondary outcome of depressive symptoms, and possible mediators (i.e., psychological stress, circadian disruption, inflammation) as assessed by standard measures.

Aim 2: To measure the impact of the YST versus the AC on daily assessments of fatigue, depressive symptoms, and proposed mediators in the same trial and explore relationships among daily and standard assessments.

Aim 3: To qualitatively assess perceived efficacy of the YST and AC and acceptability of new methodology through semi-structured interviews in a subset of 20-40 participants.

Design and Outcomes

We propose a prospective stratified randomized controlled pilot study of the preliminary efficacy of YST as compared to AC on fatigue, depressive symptoms and possible mediators in a sample of people with GI cancer receiving first-line chemotherapy.

Standard recalled assessments of fatigue, depressive symptoms and possible mediators will be collected at four time points (baseline, mid-intervention, post-intervention, 4-week follow-up). Participants will also be asked to complete daily assessments of outcomes, mediators, and adherence to home practice of the intervention via an automated daily survey and wear a wrist actigraphy device for two weeks before and two weeks following the interventions. Inflammatory cytokines will be collected along with patients regularly scheduled blood draws at weeks 2 and 10 and a semi-structured interview conducted after completion of all assessments.

Interventions and Duration

The YST intervention will be administered individually in the clinic during chemotherapy infusions and patients will be encouraged practice the YST daily at home. Chemotherapy infusions follow a standardized treatment regimen that is given during biweekly visits. Dr. Sohl developed the YST for a prior study to teach the key

elements of yoga in a manner that would accommodate patients' needs and reduce barriers to adherence during chemotherapy. The YST intervention has been modified for this study to consist of four 30 minute in-person sessions (weeks 2, 4, 6, 8) that instructs skills to enhance mindfulness and promote relaxation.

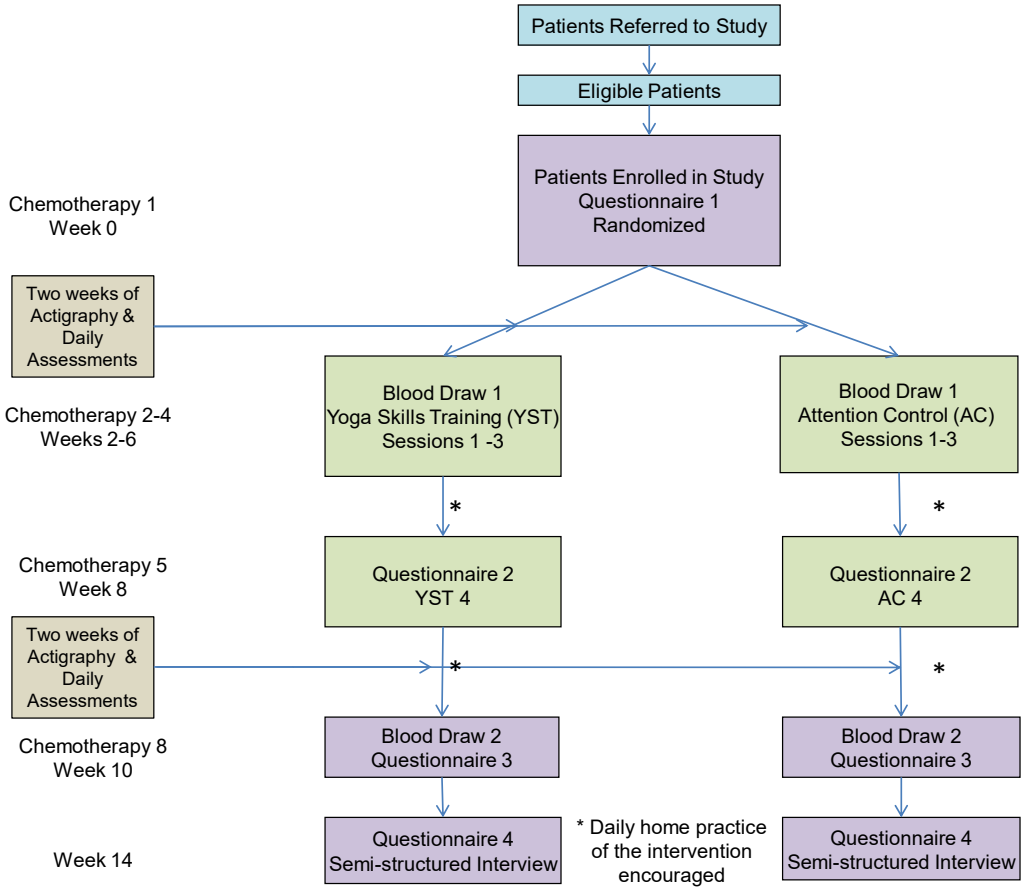
An empathic attention control group will be employed as the AC to account for the added attention and efficacy expectations of the YST as used in previous studies.[1–31–31–3]

In addition, the interventionist will recommend that the patients write brief diary entries daily at home. The number of sessions with a professional, recommended home practice, and home assessments will also be matched to the YST.
The total length of time each participant will be on study is approximately 14 weeks (see Study Schema).

Sample Size and Population

The target population is 44 participants, 22 in each group. Randomization will be stratified by type of cancer (colon, rectal/other better prognosis GI cancers, poorer prognosis cancers) and cancer stage (localized stages II/III or metastatic stage IV) to minimize differences between groups (6 strata total). We will add cancers of the small intestine, anus and appendix to our existing rectal cancer strata since the survival rates are similar. The cancer types with poorer prognoses will be put into the new strata (with <50% 5-year survival rate; cancers of the esophagus, stomach, pancreas, gallbladder, liver).

Study Schema



1. STUDY OBJECTIVES

1.1 Primary Objective

- To conduct a pilot randomized controlled trial of the YST versus an AC group among adults with gastrointestinal (GI) cancers receiving chemotherapy to determine preliminary efficacy for the primary outcome of fatigue, secondary outcome of depressive symptoms, and possible mediators (i.e., psychological stress, circadian disruption, inflammation) as assessed by standard measures.

  Hypothesis: The YST will show trends for reducing fatigue and depressive symptoms as assessed with standard recalled measures to a greater degree than the AC and these reductions will be associated with decreases in mediators.

1.2 Secondary Objectives

- To measure the impact of the YST versus the AC on daily assessments of fatigue, depressive symptoms, and proposed mediators in the same trial and explore relationships among daily and standard assessments.

- To qualitatively assess perceived efficacy of the YST and AC and acceptability of new methodology through semi-structured interviews in a subset of 20-40 participants.

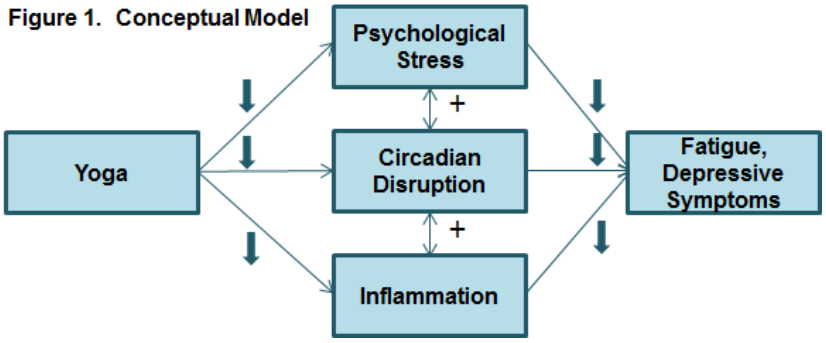
2. BACKGROUND AND RATIONALE

2.1 Background on Condition, Disease, or Other Primary Study Focus

Burden of fatigue and depressive symptoms in gastrointestinal cancers is high. Gastrointestinal (GI) cancers are among the most prevalent cancers for both men and women,[4] and the number of GI survivors continues to increase.[5–7] Fatigue, ‘‘a subjective state of overwhelming and sustained exhaustion and decreased capacity for physical and mental work that is not relieved by rest,”[8] is reported by a majority (>50%)[9,10] of patients with GI cancers, co-occurs with other common symptoms such as depression (>30% in patients receiving chemotherapy),[11–13] and is associated with a decline in post-treatment quality of life.[14,15] There is overlap in some methods for assessing fatigue and depressive symptoms; however, these symptoms remain moderately correlated even when commonalities are removed.[33] There is also considerable evidence showing that fatigue and depression are distinctly associated with other variables such as quality of life.[16–18] Further, although chemotherapy is efficacious for increasing survival,[19] it leads to increases in fatigue and depressive symptoms[20,21] such that symptoms peak approximately 3-5 days following treatment and then improve;[22–24] however fatigue and depressive symptoms do not return to pretreatment levels in a substantial subset of patients (20-80%).[25–29] Fatigue and depressive symptoms experienced during treatment are associated with subsequent symptoms.[16] Thus, it is important to address elevations of fatigue and commonly co-occurring depressive symptoms during chemotherapy to improve quality of life in patients with GI cancers.

Importance of shared biobehavioral mediators of fatigue and depressive symptoms. The biobehavioral conceptual framework and data[23,30–36] suggest that fatigue and depressive symptoms tend to co-occur because they may share underlying mechanisms including psychological stress, circadian disruption (i.e., an altered ratio of nighttime activity to daytime activity) and inflammation.[34,37,38] Figure 1 illustrates the potential relationships among these variables using a biobehavioral framework. Data support that psychological stress in cancer patients is associated with fatigue, depressive symptoms, circadian disruption and inflammation.[30,31,33,39] Cancer and its treatment can also lead to circadian disruption, which is associated with fatigue in GI cancer patients,[36] and fatigue and depressive symptoms during chemotherapy.[23,34,35] Further, evidence suggests that circadian disruption precedes fatigue and depressive symptoms.[23,40] Data also show that increases in inflammation (i.e., sTNF-R1, IL-6) specifically during treatment for gastrointestinal cancer is related to changes in fatigue and other symptoms (e.g., distress).[10]

Figure 1. Conceptual Model



2.2 Study Rationale

Preliminary efficacy of yoga for fatigue and depressive symptoms. Despite the high symptom burden, there are few behavioral interventions designed for GI cancer patients that aim to proactively improve fatigue and depressive symptoms during treatment.[41,42] Guidelines for managing cancer-related fatigue include non-pharmacologic and pharmacologic interventions that target fatigue itself, comorbid medical conditions and coexisting symptoms (e.g., depressive symptoms).[43] Both psychological and exercise interventions show efficacy for reducing fatigue and depressive symptoms and reviews suggest that a combined approach may be optimal.[29–32] However, most existing interventions for GI cancer patients do not use a combined approach.[41,42] One intervention designed for a heterogeneous group of cancers did apply a combined approach during chemotherapy, yet only found efficacy for depressive symptoms and not fatigue.[44] Yoga utilizes a combined approach and has shown efficacy for reducing fatigue and depressive symptoms when implemented as group classes primarily in patients with breast cancer though has not been investigated when implemented during chemotherapy except for in my Preliminary Research.[45,46] The key practices taught by yoga are meditation, body movements, and breathing techniques.[47] Therapeutic applications of yoga can target the instructed practices specifically to a goal, such as fatigue, which may improve upon effects found from more general strategies used thus far.[44] This notion is supported by a systematic review that revealed that behavioral interventions targeted to specifically address fatigue have increased efficacy.[48] Although the optimal dose of yoga is

unknown, the greatest improvements in fatigue were found in cancer survivors who practiced yoga an average of three times per week[49] and a review of exercise interventions (including yoga) during chemotherapy found that 90-120 minutes of moderate activity per week was better than higher doses.[50] Further, ~20 minutes of home yoga practice per day was associated with an improvement in next day fatigue.[51] Therefore, a reasonable suggested dose for yoga during chemotherapy would be 3-6 times per week for about 20 minutes per session. In summary, yoga is a promising intervention that incorporates a combined and targeted approach for reducing fatigue and depressive symptoms during chemotherapy that has yet to be investigated in patients with GI cancers.

Proposed mediators of the effect of yoga on fatigue and depressive symptoms. Reviews of yoga research call for the investigation of mediators to explain how yoga influences cancer-related outcomes such as fatigue and depressive symptoms.[52] The Self-regulation Framework can be applied to understand the efficacy of behavioral integrative medicine interventions such as yoga.[53] This framework posits that people are able to consciously alter their cognitive (e.g., mindfulness), emotional (e.g., feelings of relaxation) and behavioral (e.g., breathing) responses to various experiences (e.g., psychological stress from cancer and its treatment) to obtain desired goals (e.g., reduced fatigue).[54,55] Conscious attention to and awareness of the present moment, or mindfulness, is proposed to be the first step in the self-regulation process.[56] Yoga aims to increase mindfulness and promote relaxation to strengthen patients' ability to regulate their responses. There is evidence supporting that yoga reduces psychological stress,[57] and improves subjective and objective sleep quality (a component of circadian disruption).[58,59] Further, inflammatory cytokines are theoretical biomarkers of effective self-regulation[60] and there is some evidence that yoga reduces inflammation (e.g., IL-6, TNF-α).[61–64] Therefore, further study of yoga for reducing fatigue is warranted.[21]

The proposed yoga intervention, Yoga Skills Training (YST), will be implemented in the clinical setting to be inclusive of patients most in need of intervention. Implementation of the proposed YST individually in the clinical setting challenges the current paradigm in the United States that typically implements yoga as group classes. A study that recruited cancer patients to group yoga classes found that there were some common barriers to participating in yoga classes including, transportation, scheduling, being too busy or too sick.[58] This was important to consider in this study design because such a large portion of cancer patients travel long distances for treatment (i.e., 83% of colorectal cancer patients treated at Vanderbilt-Ingram Cancer Center travel more than 10 miles for treatment and 48% travel 50 miles or more).[65] Patients' experience of fatigue was also associated with attending fewer yoga classes in another study.[66] Therefore, patients who are burdened by fatigue or depressive symptoms during chemotherapy may be unintentionally excluded from yoga interventions due to feasibility issues. The proposed 30-minute YST can be taught to 2-3 participants in the time generally allocated to one yoga class. Therefore, the number of participants who attend each class is important to consider. In summary, the proposed YST is designed to lessen identified barriers to

participation by integrating YST into patients' already scheduled visits for chemotherapy. So far, only preliminary research has been conducted to explore if yoga can be safe and efficacious when applied in clinical settings related to cancer care.[62,67] Yet, therapeutic yoga is traditionally implemented individually.[68] Data supporting the efficacy of the YST would encourage a shift in the practice of implementing yoga primarily as a complementary modality to integrating yoga during clinical cancer care to broaden the population of patients who may benefit.

Daily measurement of fatigue and depressive symptoms will more accurately detect efficacy than more commonly used recalled assessments. Fatigue and depressive symptoms are generally assessed in intervention studies through retrospective patient-reported outcomes (e.g., "how much fatigue have you experienced in the past 7 days").[69,70] However, assessment over a week's time period is likely to miss the acute variation in the experience of symptoms and not capture the influence of an intervention on fatigue at its worst 3-5 days after chemotherapy infusions.[23] That is, daily symptom assessment can improve upon recalled assessments by elucidating the immediate effect of an intervention on the trajectory of symptoms following chemotherapy. Daily diaries are one method for measuring an experience in a participant's natural setting with low patient burden.[71] Fatigue and depressive symptoms will be assessed daily to reduce recall bias and enable detailed analyses of how experiences interrelate on a daily basis.[71] Few studies have utilized daily measures of chemotherapy-related symptoms[23,24,72] and this study will be the first to evaluate the impact of an intervention on daily fatigue and depressive symptoms during chemotherapy for GI cancers.

Assessing the impact of yoga on biobehavioral mediators during chemotherapy is also novel. The impact of yoga on psychological stress, circadian disruption, and inflammation during chemotherapy has not been investigated. Two pilot studies by the same research team have utilized daily assessment to evaluate the impact of yoga on "positive" therapeutic processes (i.e., invigoration, acceptance, relaxation), however, psychological stress, circadian disruption and inflammation were not assessed.[51,73] There is some support for the association between yoga and psychological stress,[57,74]objectively measured rest,[59] and inflammation,[61–64] but these relationships have not been explored daily during chemotherapy.

Preliminary Intervention Effects of the YST. Dr. Sohl developed an initial protocol for implementing the YST with patients undergoing chemotherapy for ovarian cancer.[75] Data from seven women who participated in the YST during chemotherapy showed an immediate effect. Women completed two Visual Analogue Scale items of anxiety and relaxation immediately before and after the YST. Anxiety decreased and relaxation increased after the YST. Effect sizes were large (anxiety, d=-0.82; relaxation, d=0.83). Hospital staff did not find the YST burdensome and it was feasible to conduct the YST in a clinical setting. In addition, this study supported the safety of implementing the YST during chemotherapy. Minimal risk including potential for muscle soreness from the gentle movements or emotional discomfort from breathing and meditation practices is expected from participating in the YST.

Preliminary Feasibility of the YST for GI Cancers. Dr. Sohl also conducted a randomized pilot trial of the YST as compared to an attention control group for patients receiving chemotherapy for colorectal cancer. Of the 29 patients approached, 15 (51.7%) agreed to participate with interest from both men (60%) and women (40%). Most (80%) of the in-person intervention sessions (YST or active control) were completed with missed sessions due to patients not receiving chemotherapy. The active control consisted of empathic attention. Thus, these preliminary data support feasibility for recruitment and randomization. Based on what the PI learned from this initial pilot, and with input from my current mentors and other experts, we plan to build upon this previous YST by implementing more robust and innovative measurement (i.e., daily assessments of symptoms, objective measure of circadian disruption, mixed-methods follow-up assessment) and enhancing the YST intervention (i.e., more targeted to fatigue, attention to treatment fidelity, focused on adherence to home practice).

3. STUDY DESIGN

We propose a prospective stratified randomized controlled pilot study in a sample of GI cancer patients receiving first-line Fluorouracil (5FU)-based chemotherapy (5FU-based chemotherapy is the standard treatment for all patients with colorectal cancers and most patients with other gastrointestinal cancers). This study will assess preliminary efficacy of YST on the primary outcome of fatigue, secondary outcome of depressive symptoms, and possible mediators (i.e., psychological stress, circadian disruption, inflammation) as assessed by standard measures. Secondary objectives are to measure the impact of the YST versus the AC on daily assessments of fatigue, depressive symptoms, explore relationships among daily and standard assessments, and explore mediators. At study completion, the first 20-40 participants will be selected for semi-structured interviews to discuss perceived impact of the intervention, and adherence to home practice, and acceptability of measures. Overall, the study is designed to help inform a larger future study.

Standard recalled assessments of fatigue, depressive symptoms and possible mediators will be collected at four time points (baseline, mid-intervention, post-intervention, 4-week follow-up). Participants will also be asked to complete daily assessments of outcomes, mediators, and adherence to home practice of the intervention via an automated daily survey and wear a wrist actigraphy device for two weeks before and two weeks following the interventions. Inflammatory cytokines will be collected along with patients regularly scheduled blood draws at weeks 2 and 10 and a semi-structured interview conducted after completion of all assessments.

The YST intervention will be administered individually in the clinic during chemotherapy infusions and patients will be encouraged practice the YST daily at home. Chemotherapy infusions follow a standardized treatment regimen that is given during biweekly visits. Dr. Sohl developed the YST for a prior study to teach the key elements of yoga in a manner that would accommodate patients' needs and reduce barriers to adherence during chemotherapy. The YST intervention has been modified for this study to consist of four 30 minute in-person sessions (weeks 2, 4, 6, 8) that

instructs skills to enhance mindfulness and promote relaxation.

An empathic attention control group will be employed as the AC to account for the added attention and efficacy expectations of the YST as used in previous studies.[1–3] [1–3] In addition, the interventionist will recommend that the patients write brief diary entries daily at home. The number of sessions with a professional, recommended home practice, and home assessments will also be matched to the YST.

The total length of time each participant will be on study is approximately 14 weeks. The enrollment period for the trial is expected to continue for 30 months.

4. SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Inclusion Criteria

Participants must meet all of the inclusion criteria to participate in this study.

- Adults (≥21 years of age)
- Scheduled to receive first-line Fluorouracil (5FU)-based intravenous chemotherapy treatment for a gastrointestinal cancer (stages II-IV)
- Has an Eastern Cooperative Oncology Group performance status of ≤1
- Ability to understand and the willingness to sign an informed consent document in English

4.2 Exclusion Criteria

All candidates meeting any of the exclusion criteria at baseline will be excluded from study participation.

- Has a self-reported history of diagnosed sleep disorders (e.g., obstructive sleep apnea, insomnia), comorbidities associated with poor sleep or fatigue (e.g., chronic fatigue syndrome), or a job with night shifts.

4.3 Study Enrollment Procedures

Individuals scheduled to receive first-line 5FU chemotherapy for a gastrointestinal cancer will be recruited from the Comprehensive Cancer Center at Wake Forest University (CCC-WFU) and the Vanderbilt Ingram Cancer Center (VICC; site-specific protocol, closed to recruitment). To identify potential patients, a study team member (STM) will screen participants using electronic medical records containing patients' schedules and communicate with attending physicians regarding patients' potential eligibility for trial. Subject recruitment will be documented in a Screening Log including reasons for ineligibility, eligible patients approached, number who declined participation, and number successfully recruited.

If the patient is interested, the STM will approach the patient at a clinic visit or call the patient to explain the protocol, answer questions, further determine eligibility, and discuss informed consent. After making sure the patient clearly understands the study

procedures and agrees to follow them, the patient will be asked to sign the informed consent form either in person or remotely (Appendix A: Informed Consent Document). If signed remotely, patients will be asked to mail, or fax the form back to us, as well as bring the original with them to their next clinic visit. A copy of the consent form will be given to the participant in person the next time they are in clinic, and the original copy will be kept in the participant's file.

Eligible participants enrolled in the study will be randomized after baseline assessments to YST or AC at week 0.

Randomization. Eligible, consented, and enrolled participants will be randomized to YST or AC. To control for type and stage of cancer, randomization will occur within both type (colon, rectal/other better prognosis GI cancers, poorer prognosis cancers) and stage (localized stages II/III or metastatic stage IV). Randomization (1:1) lists within each strata will be generated via a permuted block program developed and executed by the study biostatistician with blocks of random sizes between 2 and 6. The randomization lists will be held by a STM (not involved with data collection) who will allocate each participant to study group. Once assigned, details about that arm will be revealed to the PI for study coordination purposes.

5. STUDY INTERVENTIONS

5.1 Interventions, Administration, and Duration

Active Intervention. The Yoga Skills Training (YST) intervention will be administered individually in the outpatient clinic while patients are in the chair during outpatient chemotherapy sessions and patients will be encouraged practice the YST daily at home. First-line 5FU-based chemotherapy for gastrointestinal cancers is typically given during biweekly visits. Dr. Sohl developed the YST for a prior study to teach the key elements of yoga in a manner that would accommodate patients' needs and reduce barriers to adherence during chemotherapy.[59] The YST intervention consists of four 30 minute in-person sessions (weeks 2, 4, 6, 8) that instructs skills to enhance mindfulness and promote relaxation: (a) *Awareness* – noticing the current state and establishing relaxed breathing – 5 minutes; (b) *Movement* - 7 minutes of gentle movements coordinated with the breath (such as raising and lowering the arms); (c) *Breathing Practice* - 3 minutes of inhaling cool air as if through a straw; (d) *Meditation* - 5 minutes of focus on letting go of physical and mental tension. In addition, the first five minutes of the YST will address any questions and inquire about the participant's current physical status. The last five minutes will be used to review a handout describing the YST (Appendix B: YST Home Practice Guide; Appendix C: YST Diary) and to encourage participants to practice daily with strategies to increase adherence to home practice described later in this section. Participants will also be given an audio recording of the YST and devices to play the recording. The content of the YST was informed by the Dr. Sohl's training from the Integral Yoga Academy's Yoga for People with Cancer Teacher Training taught by Jnani Chapman, RN, RYT, the Urban Zen Integrative Therapy training, and was modified for this study to further target fatigue and depressive symptoms by

consulting with expert yoga therapists from the Krishnamacharya tradition (i.e., led by Amy Wheeler, Ph.D). Each session will contain the same content, but the movement will be individualized based on ability and level of energy that day. Self-compassion will be highlighted throughout the YST and any medical restriction can be accommodated. All yoga instructors (i.e., interventionists) will have completed accredited yoga teacher training programs and be experienced teaching patients with chronic illness. Minimal risk including potential for muscle soreness from the gentle movements or emotional discomfort from breathing and meditation practices is expected from participating in the YST.

Attention Control (AC). An empathic attention control group will be employed as the AC to account for the added attention and efficacy expectations of the YST as used in previous studies.[1–3] In addition, the interventionist will recommend that the patients write brief diary entries daily at home as used as a control condition in another previous study (Appendix D: AC Home Diary).[76] The AC will not include instruction of movement, meditation or breathing practices, which are the active ingredients of the YST. The location, number of sessions with a professional, recommended home practice, and home assessments will also be matched to the YST. The AC will be implemented by an individual with a background conducting research in a medical setting who will be trained to create and maintain a relationship by using techniques of active listening, reflection of statements, and avoiding negative judgments. This individual will spend approximately 30 minutes with patients for four sessions while they are undergoing chemotherapy. S(he) will utilize standardized instructions to prompt the patient as adapted from previous studies[2,76,77]: "What were some of the events or circumstances that affected you in the past two weeks?" Patients will be encouraged to ''discuss one experience at a time, even if it means talking about the same experience each session. However, if you find that you have discussed it in adequate detail, please move on to a new topic.'' The instructions for daily diary entries will be, "What were some of the events or circumstances that affected you in the past day? Think back over the past day and write down on the lines below up to five events that had an impact on you."[76] Minimal risk including potential for emotional discomfort from disclosing personal experiences is expected from participating in the AC.

5.2 Handling of Study Interventions

Participants will be told that both groups offer programs to support their experiences in coping with chemotherapy to match efficacy expectations. Information about both arms will be revealed to participants after completion of data collection.

Treatment Fidelity. A number of steps will be taken to ensure treatment fidelity.[78–80] Dr. Sohl will train interventionists in implementation of the YST and AC during an initial four hours of training and monthly meetings. Dr. Sohl will remain an objective observer in order to develop a system for establishing treatment fidelity. One primary YST and AC interventionist will implement the interventions and at least two additional interventionists trained in the intervention protocol will serve as back-ups. The interventionists will complete a written test to confirm their understanding, be

video recorded during all sessions (using a small device that will not record the patient or anyone else present) with 10% of the recordings randomly selected for Dr. Sohl's review, and document each in-person session with a checklist (Appendix E: Treatment Fidelity Forms). The checklist will be also used to evaluate consistency of implementation.

Adherence Strategies. To optimize adherence to home practice interventionists will be trained to adopt brief coaching methods based on motivational interviewing as used to encourage yoga practice and walking in other studies of cancer patients.[49,81] Specifically, the interventionists will ask open-ended questions to inquire about goals, specific times planned for home practice, and strategies to ensure home practice of the interventions. Confidence in the ability to practice will be verbally assessed and reports of low confidence discussed.

5.3 Concomitant Interventions

5.3.1 Allowed Interventions

All participants will continue with routine treatment of medical conditions including chemotherapy and medications.

5.3.2 Required Interventions

No additional interventions are required except for those propose in the protocol.

5.3.3 Prohibited Interventions

There will be no prohibited medications among patients in this study. Prior approval of participation in other behavioral intervention studies is required.

5.4 Adherence Assessment

Adherence will be assessed by: (1) participation in-person sessions (i.e., number of sessions completed); (2) number of components completed at each in-person YST session; (3) and days of intervention home practice (see Section 6.2 - Description of Evaluations). Instructors will directly observe and document adherence to in person sessions. We will consider high adherence to protocol if participants complete 75% of the planned in-person sessions and 3 or more days of home practice per week in between in-person sessions.

6. STUDY PROCEDURES

6.1 Schedule of Evaluations

Assessment	Screening: (Day-14 to Day -1)	Consent Enrollment, Randomization (Day 0)	Daily Survey (W0-W2)	AC or YST 1 (W2)	AC or YST 2 (W4)	AC or YST 3 (W6)	AC or YST 4 (W8)	Daily Survey (W8-W10)	(W10)	Follow-up (W14)	Person(s) Responsible
Inclusion/Exclusion Criteria	X										PI, STM
Permission of Oncologist	X										PI, STM
Informed Consent Form		X									PI, STM
Enrollment/Randomization		X									PI, STM
Demographics		X									STM
Clinical Data		X								X	STM
Questionnaire		X					X		X	X	STM
Automated Daily Survey			X					X			Participant
Actigraphy			X					X			Participant
Treatment Fidelity				X	X	X	X				PI, Interventionist
Intervention Home Practice				X				X			Participant
Adherence		X	X	X	X	X	X	X	X	X	PI
Blood Draws				X					X		STM
Adverse Events				X	X	X	X				Interventionists,[A] PI,[B] STM[C]
Interview										X	Trained Facilitator

Note. AC = Attention Control; YST = Yoga Skills Training; PI = Principal Investigator; STM = Study Team Member

[A] Interventionists will note any adverse events that occur during the intervention or reported by patients during home practice.

[B] The PI will review interventionists' notes and identify any AE's that need to be captured.

[C] Other Study Team Members (e.g., Research Nurses) will report ratings of 3 or higher on the suicide item from the depression assessment (corresponding with Weeks 0, 8, 10 and 14). They will not collect any additional information related to adverse events.

6.2 Description of Evaluations

Recalled assessments will be collected at four time points (baseline, mid-intervention, post-intervention, 4-week follow-up; Appendix F: Chart Review Form and Questionnaires) and a semi-structured interview conducted after completion of all assessments (either in person or by telephone; Appendix G: Semi-Structured Interview Guide). To minimize burden, all assessments via recalled questionnaires and interviews will be scheduled to coincide with the patients' appointment for chemotherapy. Therefore, sequencing of each patient's assessments will be based on the timing of the respective patient's first completed chemotherapy visit. The standard chemotherapy timing is every two weeks. The randomized study condition will commence with the second chemotherapy visit. Given that there may be slight personal modifications to the standard schedule, we have proposed a design that will attempt to control for the possible effect of chemotherapy schedule on outcomes. If a chemotherapy visit is rescheduled for within two weeks of the standard schedule, the intervention will occur at that next visit (and all following assessments will then follow the subsequent standard chemotherapy schedule). If the rescheduled chemotherapy visit is more than two weeks later, the in-person study intervention session for that participant will not occur, the assessments will be mailed to the participant for completion, and this will be documented as an aspect of treatment fidelity.

Participants will also be asked to complete daily assessments of and adherence to home practice of both interventions for two weeks before and after the intervention via an automated daily survey and wear a wrist actigraphy device. Participants will also be asked to complete daily assessments of outcomes, mediators, adherence to home practice of the intervention for two weeks before and after the intervention via an automated daily survey (Appendix H: Daily Survey) and wear a wrist actigraphy device. Participants will be given the choice to respond to the automated daily diary via an interactive voice response system (IVRS) or internet survey hosted through a REDCap platform that will verify the date and time of assessments. IVRS and internet surveys have been successfully applied in similar research to assess daily symptoms in people with cancer[73,82,83] and may improve compliance to assessments as compared to more commonly used paper daily diaries.[84] Participants will be asked to complete surveys in the evening. Those who choose to complete the survey via IVRS will be called at approximately 6:00pm each evening (unless the participant indicates another strong time preference) and have the option to call back before they go to sleep. A paper guide with response options for the daily survey will be provided to improve comprehension over the telephone. If participants do not complete the first two surveys a STM will call them to confirm receipt of calls. If for any reason the automated survey system is not available, a STM will call the patient to complete the same survey. Participants will also be given a wrist actigraphy device and instructions for its use to measure circadian disruption. Instructions for use will be guided by Dr. Malow and Dr. Kumar.

Inflammatory cytokines will be collected via EDTA plasma samples by a Licensed Practical Nurse or phlebotomists along with patients regularly scheduled blood draws at weeks 2 and 10. Although this method may not account for possible variation in circadian patterns release of some cytokines, cytokines were similarly assayed in another study,

which associated elevated cytokines to increased fatigue during chemotherapy.[10] All assays will be conducted by the Cytokine Core Laboratory led by Dr. Nicklas.

Semi-structured interviews will be conducted face-to-face or by telephone and audio recorded by a trained facilitator for approximately 45 minutes.[85] If the interview is implemented by telephone, no personal health information will be revealed unless speaking directly to the participant. Additional study process variables will also be tracked (e.g., recruitment, adherence to in-person intervention sessions, safety) and participants will be asked for feedback regarding reasons for declining participation and dropping out of the study.

Measures

Demographics. Age, race/ethnicity, marital status, education level, ability to pay for the basics, alcohol/substance use and malnutrition status will be self-reported at baseline.[86]

Clinical Data. Cancer type, chemotherapy regimen, stage of disease, recurrence status, receipt of other treatments, days since surgery, height, and weight will be abstracted from medical charts at baseline. Any chemotherapy dose modifications or symptoms related to dehydration (e.g., diarrhea) and medications for fatigue, sleep, anemia, depressive symptoms, and pain will be abstracted at follow-up.

Questionnaire

- **Fatigue (recalled)** "in the past seven days" will be assessed with the 7-item measure of Fatigue from the Patient-Reported Outcomes Measurement Information System **(**PROMIS)-Cancer.[87,88] Higher scores indicate more fatigue.
- **Depressive Symptoms (recalled)** will be assessed with the standadized10-item PROMIS-Cancer Depressive symptoms short-form.[89]
- **Psychological Stress (recalled)** will be assessed by the 10-item Perceived Stress Scale (PSS).[90] The PSS has 2 factors (stress and counter stress).[91]
- **Regulation of Psychological Stress (recalled)** will be determined by ratings on four of the seven factors of the Cancer Behavior Inventory[92], which assess self-efficacy for stress management ($\alpha = 0.86$), coping with treatment-related side-effects ($\alpha = 0.82$), accepting cancer/maintaining positive attitude ($\alpha = 0.86$), and affective regulation ($\alpha = 0.81$).
- **Circadian disruption (recalled)** will be assessed with measures of activity and rest. Activity will be measured using the 3-item Godin's leisure score index (LSI),[93] previously used with GI cancer patients during chemotherapy.[94] Rest will be assessed with the 8-item PROMIS sleep disturbance short-form.[87]
- **Efficacy Beliefs.** Participants will be asked after experiencing their assigned intervention how strongly they believe that it will improve their fatigue and depressive symptoms as implemented in another randomized controlled trial during chemotherapy[95] with adapted items.[45]
- **Outcome Expectancies (specific).** Using items adapted from other studies, participants will be asked how strongly they believe that various modalities

including moderate physical activity, gentle physical activity (e.g., stretching), a mind-body practice, writing, counseling or medication would improve their fatigue and mood during chemotherapy.[95]

- **Outcome Expectancies (general).** Generalized outcome expectancies will be assessed by the Life Orientation Test-Revised.[96]

Daily Survey

- **Fatigue and Depressive Symptoms (daily)** "in the last day" will be assessed with 3 items selected from the PROMIS measures of fatigue and depression validated for use in daily diaries.[97]
- **Psychological Stress (daily)** will be assessed with two items from the 4-item PSS[90] that would be on the same factor to optimize internal consistency.[91] The PSS has been successfully applied daily.[98]
- **Regulation of Psychological Stress (daily)** will be assessed with the 3-item serenity subscale from the Positive and Negative Affect Schedule-Expanded Form.[99]

Actigraphy (Circadian Disruption - daily) will be assessed with actigraphy, a non-intrusive alternative to the traditional polysomnogram when monitoring sleep in humans.[100] The Actiwatch Spectrum model actigraph will be worn for two weeks at a time and uses an accelerometer to measure participant movement. This watch-like device has the ability to measure rest/activity patterns in a natural setting. Circadian disruption is defined as a ratio of nighttime activity to daytime activity with higher scores indicating greater circadian disruptions. A similar device and the same ratio has been used in patients during chemotherapy.[23] Participants will also self-report their bedtimes and rising times using the daily automated survey to facilitate interpretation of actigraphy data.[23]

Treatment Fidelity. Each in-person session will be documented with a checklist and 10% of these sessions will be observed to verify treatment fidelity.

Intervention Home Practice. Throughout the intervention, participants will keep daily paper logs of their home practice.[101] In addition, one item will ask via the daily automated survey how many minutes participants practiced the intervention that day for two weeks after completion of the intervention as assessed in another yoga study.[51]

Adherence. Percent of all assessments completed and the timeliness of completion will be tracked.

Blood draws (Inflammation). Inflammatory cytokines (i.e., IL-6, sTNF-R1, TNF-α) that have been associated with fatigue during treatment for gastrointestinal cancer [7] and influenced by yoga practice[61–64] will be measured in plasma extracted from whole blood drawn during regularly scheduled clinical blood draws. All assays will be conducted by trained technicians in the Cytokine Core laboratory directed by Dr. Nicklas. IL-6 and TNF-α will be measured using high-sensitivity Quantikine® immunoassay kits (IL-6:

sensitivity=0.10 pg/ml, expected detection range=0-10.0 pg/ml; TNF-a : sensitivity=0.12 pg/mL, expected detection range=0-32.0 pg/ml). In our laboratory, the inter-assay and intra-assay CVs for IL-6 are 7.5% and 4.5%, respectively, and for TNF-a are 11.8% and 6.2%%, respectively. IL-1Ra will be measured using standard Quantikine® kits (sensitivity=14 pg/ml, expected detection range=0-3000 pg/ml). All samples will be assayed in duplicate and the average of the two measures will be used for data analyses. To eliminate variability due to reagent conditions, we will pre-order the same lot number for all kits needed for a particular assay. In addition, we run all sample time points from individual participants on the same assay plate to reduce intra-assay variation. We will include an internal laboratory control on each 96-well plate. To date, inter-assay variability in this internal control has been low (CV<15%) in this laboratory, indicating that cytokine levels can be measured reliably over time. However, if the value for this control exceeds this 15% range, we will re-run the samples on that plate.

Interview (Qualitiative Feedback). A semi-structured interview will also implemented after all other data collection is complete to solicit feedback on the acceptability of data collection methods, the participants' experience with both the interventions (e.g., expected efficacy, what was useful), and barriers and facilitators to home practice.

6.2.1 Screening Evaluation

Consenting Procedure

If the patient is interested and referred by the physician, the PI or a STM will approach the patient at a clinic visit or call the patient at home to explain the protocol, answer questions, determine eligibility, and discuss informed consent (Appendix I: Recruitment Script; Appendix J: Recruitment Flyer). After making sure the patient clearly understands the study procedures and agrees to follow them, the patient will be asked to sign the informed consent form either in person or remotely. If signed remotely, patients will be asked to mail or fax the form back to us, as well as bring the original with them to their next clinic visit. If consent is obtained via REDCap, an original signature will be obtained at their next clinic visit. A copy of the consent form will be given to the participant in person the next time they are in clinic, and the original copy will be kept in the participant's file.

Screening

Screening evaluations will begin once a patient is scheduled for a consultation related to receiving first-line chemotherapy for GI cancers at VICC or CCC-WFU. The allowable range of time for screening is up to one year prior to study entry and baseline assessment. Electronic medical records of patients planning to receive chemotherapy will be reviewed by a STM to identify potential patients that meet enrollment criteria. This screening will consist of (Appendix K: Eligibility Checklist):

- Review of medical history
- Review of treatment plan

We will approach patients either in person or remotely (e.g., telephone, myWakeHealth) regarding their interest in study participation. For patients interested in the study, research staff will verify eligibility through patient interview regarding medical history.

6.2.2 Enrollment, Baseline, and/or Randomization

Enrollment

Enrollment is defined as the randomization date or as the date all of the screening criteria are met and the individual agrees to participate. This enrollment date will be recorded (Appendix L: Protocol Registration Form).

Registration Procedures

All patients entered on any CCCWFU trial, whether treatment, companion, or cancer control trial, **must** be registered with the CCCWFU Protocol Registrar or entered into Oncology Research Information System (ORIS) Screening Log within 24 hours of Informed Consent. Patients **must** be registered prior to the initiation of treatment.

The following steps must be performed in order to ensure prompt registration:

1. Complete the Eligibility Checklist (Appendix K)
2. Complete the Protocol Registration Form (Appendix L)
3. Alert the Cancer Center registrar by phone, *and then* send the signed Informed Consent Form, Eligibility Checklist and Protocol Registration Form to the registrar, either by fax or e-mail.

   *Protocol Registration is open from 8:30 AM - 4:00 PM, Monday-Friday.

4. Fax/e-mail ALL eligibility source documents with registration. Patients **will not** be registered without all required supporting documents.

Note: If labs were performed at an outside institution, provide a printout of the results. Ensure that the most recent lab values are sent.

To complete the registration process, the Registrar will:

- assign a patient study number
- other appropriate actions
- register the patient on the study

Baseline Assessments

For participants who have successfully been screened for eligibility and are enrolled into the study, baseline assessments will be performed.

Demographics. Age, race/ethnicity, marital status, education level, ability to pay for the basics, alcohol/substance use and malnutrition status will be self-reported at baseline.[86]

Clinical Data. Cancer type, chemotherapy regimen, stage of disease, recurrence status, receipt of other treatments, days since surgery, height, and weight will be abstracted from medical charts at baseline.

Questionnaire: Fatigue, Depressive Symptoms, Psychological Stress, Regulation of Psychological Stress, Circadian disruption, and Outcome Expectancies

Daily Survey (weeks 0-2) will assess baseline Fatigue and Depressive Symptoms (daily), Psychological Stress (daily), Regulation of Psychological Stress (daily), bedtimes and rising times

Actigraphy (weeks 0-2) will assess baseline circadian disruption (daily)

Blood draws (Inflammation). Inflammatory cytokines will be assessed at Week 2 prior to starting the intervention.

Randomization

Randomization will occur the same day that screening is confirmed and will precede intervention initiation by approximately 2 weeks (corresponding with the timing between chemotherapy treatments 1 and 2).

6.2.3 Blinding

- Participants will be told that both groups offer programs to support their experience in coping with chemotherapy to match efficacy expectations.
- All STM will know to what arm participants are assigned. The STM collecting outcome assessments will not know which intervention each arm letter represents.
- A complete description of each study arm will be presented to participants upon their completion of all study measures (Appendix M: Thank You Letter).

6.2.4 Followup Visits

Adherence to all assessments completed will be tracked throughout the data collection period. In addition, the following treatment and followup visit assessments will be performed.

- *Weeks 2, 4, 6*
  - **Treatment fidelity** Each in-person session will be documented with a checklist.
  - **Intervention home practice.** Throughout the intervention, participants will keep daily paper logs of their home practice.
- *Week 8*

- **Treatment fidelity** the in-person session will be documented with a checklist.
- **Questionnaire:** Fatigue, Depressive Symptoms, Psychological Stress, Regulation of Psychological Stress, Circadian disruption and Efficacy Beliefs.
- **Daily survey (weeks 8-10)** will assess baseline Fatigue and Depressive Symptoms (daily), Psychological Stress (daily), Regulation of Psychological Stress (daily), bedtimes and rising times, how many minutes practiced the intervention that day.
- **Actigraphy (weeks 8-10)** will assess baseline circadian disruption (daily).

- *Week 10*
  - **Questionnaire:** Fatigue, Depressive Symptoms, Psychological Stress, Regulation of Psychological Stress, Circadian disruption
  - **Blood draws (Inflammation).** Inflammatory cytokines will be assessed.

6.2.5 Completion/Final Evaluation

The following assessments will be performed the final visit (Week 14).

- **Clinical data**. Any chemotherapy dose modifications, symptoms related to dehydration (e.g., diarrhea) and prescription medications for fatigue, sleep, anemia, depressive symptoms, and pain will be abstracted at follow-up.
- **Questionnaire:** Fatigue, Depressive Symptoms, Psychological Stress, Regulation of Psychological Stress, Circadian disruption
- **Interview (Qualitiative Feedback).** A semi-structured interview will be implemented after all other data collection is complete.

Participants who discontinue study the intervention early (e.g., due to changes in chemotherapy treatment location, who choose to withdraw participation) will require no specific evaluations. The reason for discontinuation will be documented. We will contact participants to obtain follow-up data remotely if they discontinue participation due to change in treatment location. Patients terminated from the study will undergo no further monitoring once they have stopped the study intervention.

7. SAFETY ASSESSMENTS

Expected adverse experiences for each study intervention are as follows:

Yoga Skills Training

- Emotional discomfort
- Muscle soreness

Active Control

- Emotional discomfort

Expected adverse experiences to the participant related to assessment are as follows:

- Bruising or minor swelling
- Emotional discomfort

Each interventionist will monitor and note any adverse events experienced during the interventions (e.g., patients' experience of disturbed breath, expression of physical/emotional discomfort, or request to discontinue the in-person intervention sessions). In addition, interventionists will ask participants if they experienced any problems when doing the home practices and review notes from the home practice logs. These logs will be reviewed by the interventionist at each in-person session.

If a participant reports a 3 (sometimes) or higher on the item, "I thought about suicide" from the standardized PROMIS-Cancer Depressive symptoms short-form, we will inform the participant's oncologist regarding concern for depression and need for further evaluation from a mental health specialist (psychiatrist and/or clinical psychologist) within 24 hours of receiving the questionnaire (all implemented in person with the exception of the follow-up, which may be returned by mail). We will also notify oncologists if their patient verbally reports severe depressive symptoms or suicidality during the course of the study to research staff.

Two or more adverse events attributable to the interventions will prompt modification of the protocol.

7.1 Specification of Safety Parameters

See previous section for safety parameters.

7.2 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

Overall, risks related to the interventions in this study are considered to be minimal and are addressed in the protocol and consent form. The study employs gentle seated movement, breathing and meditative practices or an empathic attention among people diagnosed with cancer[4642] who are receiving chemotherapy. Similar yoga interventions have been studied in patients with cancer with no published reports of adverse events, some of which included participants during the chemotherapy treatment period.[46] The PI conducted an initial pilot study of 7 participants with the YST during chemotherapy infusions at the Mount Sinai School of Medicine from 08/2009 – 01/2010.[75] There were no adverse events observed related to the yoga practice in this study. From 07/2011-01/13, the PI conducted a pilot study among 15 participants randomized to YST or AC during chemotherapy infusions at the CCC-WFU and observed no adverse events related to the interventions.

7.3 Adverse Events and Serious Adverse Events

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded

from the CTEP web site (http://ctep.cancer.gov**).**

'Expectedness'**: AEs can be 'Unexpected' or 'Expected' for expedited reporting purposes only.**

- **Attribution** of the AE:

- Definite – The AE **is clearly related** to the study intervention.
- Probable – The AE **is likely related** to the study intervention.
- Possible – The AE **may be related** to the study intervention.
- Unlikely – The AE **is doubtfully related** to the study intervention.
- Unrelated – The AE **is clearly NOT related** to the study intervention.

SAEs unequivocally due to disease progression are not considered SAEs for the purposes of this study and will not be reported as such.

Only AEs related to the study intervention or measures will be captured with the exception of unexpected grade 4 Grade 5 events, which will also be documented and reported.

AEs will be labeled according to severity, which is based on their impact on the patient. An AE will be termed "mild" if it does not have a major impact on the patient, "moderate" if it causes the patient some minor inconvenience, and "severe" if it causes a substantial disruption to the patient's well-being.

AEs will be categorized according to the likelihood that they are related to the study intervention. Specifically, they will be labeled definitely unrelated, definitely related, probably related, or possibly related to the study intervention.

Interventionists will document and report solicited AEs including physical or emotional discomfort. STM will also document self-reported ratings of 3 or higher on the suicide item from the PROMIS-Cancer Depressive symptoms measure. No additional unsolicited events will be systematically captured. Research staff will report AEs according to data safety monitoring plan. Events will be documented in the ORIS data entry system including date of event which will avoid double capture.

7.4 Reporting Procedures

The PI will monitor the safety of participants on an ongoing basis by inquiring about each participant's emotional and physical reactions during all regular study meetings with the interventionists and offer referrals by consulting with mentors when appropriate. The PI will initially assess if the AE is related to the study interventions as definitely, probably, possibly or unrelated. AEs reports will be distributed to the Independent Monitoring Committee (IMC) electronically via email.

The IMC will monitor and review adverse events and events that may be related to the intervention. This will include verification that, when indicated, these events have been reported to the appropriate agencies (e.g. IRB, NCCIH) and that such reports have been made in a timely manner. Non-serious adverse events will be reviewed on a quarterly basis by the IMC. The IMC will be notified of serious adverse events within 24 hours of occurrence and reviewed within 48 hours.

SAEs that are unanticipated, serious, and possibly related to the study intervention will be reported to the IMC, IRB, and the National Center for Complementary and Integrative Health (NCCIH) by sending the SAE Report Form via email (Appendix N: Adverse Event Form). The CCC-WFU Safety and Toxicity Reporting Committee (STRC) will also review unexpected grade 4 and all grade 5 events regardless of their attribution.

- Unexpected fatal or life-threatening AEs related to the intervention will be reported to the NCCIH Program Officer within 7 days. Other serious and unexpected AEs related to the intervention will be reported to the NCCIH Program Official within 15 days.
- Anticipated or unrelated SAEs will be handled in a less urgent manner but will be reported to the Independent Monitor(s), IRB, NCCIH, and other oversight organizations in accordance with their requirements. In the annual AE summary, the Independent Monitor(s) Report will state that they have reviewed all AE reports.

7.5 Follow-up for Adverse Events

AEs will be monitored by the IMC and the PI for recurrences, resolution, and ongoing toxicities that may be related to the intervention. Documentation and reporting for follow-up AEs will occur according to reporting procedures described in Section 7.4. The duration for follow-up will be for the length of the study period while participants are enrolled in the study. If non-serious adverse events are related to the interventions, then the protocol will be modified to avoid adverse events. If the frequency of non-serious adverse events is higher than anticipated or alters the benefit risk ratio, the study investigators, after conferring with IMC, will also modify the protocol. Two or more specific adverse events among participants will prompt modification of the protocol.

7.6 Safety Monitoring

The Independent Monitoring Committee (IMC) for this study is comprised of the Wake Forest School of Medicine's Institutional Data and Safety Monitoring Board members who have expertise in clinical trial methodology and conduct, biostatistics, ethics, and clinical research. The Institutional Data and Safety Monitoring Board members are not part of the key personnel involved in this grant. They are qualified to review the patient safety data generated by this study because of their unique expertise in the areas of oncology, mental health/ethics and statistics.

Study progress and safety will be reviewed quarterly (and more frequently if needed). Progress reports, including patient recruitment, retention/attrition, and AEs will be provided to the Independent Monitor(s) following each of the quarterly reviews. An Annual Report will be compiled and will include a list and summary of AEs. In addition, the Annual Report will address (1) whether AE rates are consistent with pre-study assumptions; (2) reason for dropouts from the study; (3) whether all participants met entry criteria; (4) whether continuation of the study is justified on the basis that additional data are needed to accomplish the stated aims of the study; and (5) conditions whereby the study might be terminated prematurely. The Annual Report will be sent to the Independent Monitor(s) and will be forwarded to the IRB and NCCIH. The IRB and other applicable recipients will review progress of this study on an annual basis. The PI will also send copies of signed recommendations and comments from the Independent Monitor(s) or Chair of the IMC to the NCCIH Program Officer within 1 month of each monitoring review.

8. INTERVENTION DISCONTINUATION

The intervention will be discontinued for a participant if: (1) the intervention is associated with an adverse effect for a specific participant (i.e., participant does not tolerate the intervention), (2) the participant no longer is interested or willing to receive the intervention or participate in the study, or (3) the participant's healthcare provider no longer recommends that the patient receive the intervention for medical reasons or (4) the participant no longer receives chemotherapy at designated research facility. The IMC and the principal investigator will review cases upon occurrence for discontinuation of intervention.

This study will be stopped prior to its completion if: (1) the intervention is associated with adverse effects that call into question the safety of the intervention; (2) difficulty in study recruitment or retention will significantly impact the ability to evaluate the study endpoints; (3) any new information becomes available during the trial that necessitates stopping the trial; or (4) other situations occur that might warrant stopping the trial. The PI will include an assessment of futility in the annual progress report to NIH and will consult with the study monitors to assess the impact of significant data loss due to problems in recruitment, retention, or data collection.

Participants will be followed with their permission if the study is discontinued. The duration of follow-up will be length of the proposed study. We will continue to document adverse events during the follow-up period.

9. STATISTICAL CONSIDERATIONS

9.1 General Design Issues

Inclusion of an active control group was chosen to account for Hawthorne effects, attention from a professional, and other non-specific effects. Alternate control groups considered include a wait-list control group or stretching. Specifically, the proposed empathic attention control was chosen to control for the non-specific effects of the intervention without including any of the proposed active intervention components.

Stratified randomized control design was selected for this study to enable tighter control over known influences on outcome. Statistical control via covariate analysis would not suffice. The statistical hypotheses are:

Specific Aim 1 Hypothesis

Primary: Yoga Skills Training (YST) will demonstrate clinically meaningful reduction in fatigue and depressive symptoms compared to an attention control group.

Fatigue and depression will be measured using the Patient-Reported Outcomes Measurement Information System **(**PROMIS)-Cancer specifically designed for use in cancer patients (see Section 9.5 Outcomes).

Secondary: Reductions in fatigue and depressive symptoms will be associated with decreases in mediators.

Specific Aim 2 Hypothesis: The YST will show trends for reducing levels and variability of daily fatigue and depressive symptoms to a greater degree than the AC and reductions will be associated with decreases in mediators.

Specific Aim 3*:* Qualitative data will be used to inform a larger trial.

9.2 Sample Size and Randomization

The primary purpose of this study is to inform the potential efficacy of the YST in this population. Thus, it is imperative that in this initial study, effect sizes generated from the patients who successfully complete the YST protocol be used for that efficacy assessment. Furthermore will be important to understand likely differences between the patients who do successful complete the study protocol and those who do not. Therefore, patients for whom baseline and post YST/AC completion (Week 10) are available will comprise efficacy intention-to-treat (ITT) analysis sample. We used the revised CONSORT 2010 guidelines for intention-to-treat (ITT) analysis of randomized control trials[102] in our sample considerations. Those guidelines dropped specific ITT in favor of clear descriptions of exactly who would be (or was) included in the analysis per our specification above. We also took into account considerations for minimizing missing data within the context of ITT specified by White et al.[103] We have incorporated flexible windows for the data collection in our protocol and are allowing for possible randomly missing interim assessments. Secondary analyses will be conducted to evaluate the potential differential effect of the interventions on a one-month follow-up assessment of outcomes and changes in daily assessments of fatigue, depressive symptoms, psychological stress, and circadian disruption. Further exploratory (not hypothesis testing) analyses will be conducted with the YST study group to examine the association of dose (i.e., days of in-person sessions completed plus days of home practice), outcome expectations and efficacy beliefs with changes in fatigue, depressive symptoms, psychological stress, circadian disruption, and inflammation.

Based on prior longitudinal work with patients from similar populations, we are anticipating approximately 15% dropout (from N=44). From previous research in a mixed sample of cancer patients,[89] the variability in the values of the PROMIS 7-item fatigue measure used in this study is a standardized standard deviation of 8 points (Mean t-score=53.6). Effect sizes in preliminary studies of yoga for fatigue as compared to an active control in patients with cancer range from 0.33 to 1.50.[45,104] This variability may be explained in part by study quality and patients' initial levels of fatigue.[45] We expect that daily assessments of fatigue and depressive symptoms will detect these symptoms at their nadir and thus may be more sensitive to such phenomena than recalled measures. Therefore, it is important to obtain a good estimate of the variance of fatigue in this group to use in future studies. Power calculations for a subsequent larger study will be based on clinically meaningful differences between the groups on the primary outcome using estimates of SD. With a sample size of 44, the probability is 0.80 (80% confidence) that the estimate of the standard deviation (SD) will be no more than 10% of the true population SD below the true population SD; if the SD varies by group, there is 80% confidence that the estimate of the SD is no more than 14% below the true SD.

Treatment Assignment Procedures

Eligible, consented, and enrolled participants will be randomized to YST or AC. To control for type and stage of cancer, randomization will occur within both type (colon, rectal/other better prognosis GI cancers, poorer prognosis cancers) and stage (localized stages II/III or metastatic stage IV). There is not a sample size goal within strata. Given this relatively small preliminary study, it was deemed more efficient and enabled tighter control over known influences on outcome to stratify rather than to use statistical control via covariate analysis. The other alternative would have been to use only a single type/stage of cancer, which was not feasible due to too few cases at VICC and CCC-WFU. The population of the cancer patients with the types/stages selected was sufficient at VICC and CCC-WFU to enable randomization within thus increasing generalizability potential.

Randomization (1:1) lists within each strata will be generated via a permuted block program developed and executed by the study biostatistician with blocks of random sizes between 2 and 6. The randomization lists will be held by a staff member (not involved with data collection) who will allocate each participant to study group. STM who are collecting data will not be informed of group assignment.

9.3 Definition of Populations

Per out description above, we used the revised CONSORT 2010 guidelines for intention-to-treat (ITT) analysis of randomized control trials[102] in our sample considerations. Those guidelines dropped specific ITT in favor of clear descriptions of exactly who would be (or was) included in the analysis per our specification above. We also took into account considerations for minimizing missing data within the context of ITT specified by White et al.[103] We have incorporated flexible windows for the data collection in our protocol and are allowing for possible randomly missing interim assessments. Therefore the population to whom these preliminary efficacy

findings will be generalizable to will be that represented by the sample meeting our requirements for inclusion in the ITT sample (see above).

9.4 Interim Analyses and Stopping Rules

There are no interim analyses planned for the primary and secondary outcomes in this clinical trial. Summaries of process variables (i.e., recruitment, adherence, data collection, retention, safety) will be conducted on a rolling basis as the study progresses. The PI will present data on subject accrual with research mentors and Independent Monitoring Committee (IMC). We anticipate recruitment on average of 1-2 patients per month or 18 patients in one year completing enrollment over the next 30 months. Fidelity of implementing the interventions will also evaluated during the study period. If we document fidelity less than 80% during the clinical trial, than interventionists will undergo further training with subsequent re-evaluation demonstrating sufficient fidelity.

Futility analyses for efficacy or safety will not be conducted in this pilot study. SAE's related to the intervention will suspend enrollment and/or the study intervention until a safety review is convened (either routine or ad hoc) by IMC to determine whether the study intervention should continue per protocol, proceed with caution, be further investigated, discontinued, or be modified and then proceed. If SAEs events are related to the interventions, then the relevant intervention protocol will be modified to avoid adverse events. If the frequency of non-serious adverse events is higher than anticipated or alters the benefit risk ratio as determined by the IMC and PI, the study investigators will also modify the relevant intervention protocol. Two or more specific adverse events among participants will prompt modification of the protocol.

9.5 Outcomes

The STM collecting outcome data will be masked to the participant's intervention group assignment.

9.5.1 Primary Outcome

Fatigue (recalled) "in the past seven days" will be assessed with the 7-item measure of Fatigue from the Patient-Reported Outcomes Measurement Information System **(**PROMIS)-Cancer specifically designed for use in cancer patients (item responses: 1 = never, 5 = always).[87,88] This measure was selected for the primary outcome (at 10 weeks) because it is standardized, validated in people with cancer, and PROMIS is supported by NCCIH and the National Cancer Institute.[89,105]

9.5.2 Secondary Outcomes

Depressive Symptoms (recalled) will be assessed with the standardized 10-item PROMIS-Cancer Depressive symptoms short-form, which was designed to be valid for cancer patients.[89]

Fatigue and Depressive Symptoms (daily) "in the last day" will be assessed with 3 items selected from the PROMIS measures of fatigue and depression validated for use

in daily diaries.[97] This subset of items was selected to minimize patient burden and because they were the items most sensitive to day-to-day changes. Response options are the same as in the recalled measures.

Psychological Stress (recalled) will be assessed by the 10-item Perceived Stress Scale (PSS).[90] The PSS has 2 factors (stress and counter stress) and is valid for use with cancer patients.[91]

Psychological Stress (daily) will be assessed with two items from the 4-item PSS[90] that would be on the same factor to optimize internal consistency.[91] The PSS has been successfully applied daily.[98]

Regulation of Psychological Stress (recalled) will be determined by ratings on four of the seven factors of the Cancer Behavior Inventory[92], which assess self-efficacy for stress management ($\alpha = 0.86$), coping with treatment-related side-effects ($\alpha = 0.82$), accepting cancer/maintaining positive attitude ($\alpha = 0.86$), and affective regulation ($\alpha = 0.81$).

Regulation of Psychological Stress (daily) will be assessed with the 3-item serenity subscale from the Positive and Negative Affect Schedule-Expanded Form.[99]

Circadian disruption (recalled) will be assessed with measures of activity and rest. Activity will be measured using the 3-item Godin's leisure score index (LSI),[93] previously used with GI cancer patients during chemotherapy.[94] Rest will be assessed with the 8-item PROMIS sleep disturbance short-form.[87]

Circadian Disruption (daily) will be assessed with actigraphy.[100] Circadian disruption is defined as a ratio of nighttime activity to daytime activity with higher scores indicating greater circadian disruptions.

Inflammation. Inflammatory cytokines (i.e., IL-6, sTNF-R1, TNF-α) that have been associated with fatigue during treatment for gastrointestinal cancer [7] and influenced by yoga practice[61–64] will be measured in plasma extracted from whole blood drawn during regularly scheduled clinical blood draws.

The following table provides a summary of which study week study constructs will be assessed.

Study Constructs and Times Measured

Weeks	**0**	**0-2**	**8**	**8-10**	**10**	**14**
Outcomes						
Fatigue (**primary in bold text**)	R	Daily	R	Daily	**R**	R
Depressive Symptoms	R	Daily	R	Daily	R	R
Mechanisms						
Psychological Stress	R	Daily	R	Daily	R	R
Regulation of Psychological Stress	R	Daily	R	Daily	R	R
Circadian Disruption	R	Daily	R	Daily	R	R

Inflammation		√		√	
Process					
Intervention Home Practice		*	Daily		
Outcome Expectancies	√				
Efficacy Beliefs		√			
Adherence		All Measures			
Qualitative Feedback					S
Descriptive					
Demographic/Clinical	√				√

R = recalled assessment; S = semi-structured interview; √ = collected

*Paper diary will be kept throughout the intervention

9.6 Data Analyses

SAS will be used for statistical analysis. Graphical and descriptive statistical methods will be applied to examine the shapes of study data distributions and need to transform, if necessary, for inferential analyses. Per descriptions above, analyses will be conducted using intention-to-treat principles as stated in the CONSORT 2010 guidelines[102] and flexible protocol elements to minimize missing outcome data.[103] Missing data are expected to be of two types: 1) nonrandom (death, deteriorating condition, or other lost-to-follow-up) and 2) random (inability to make it into the clinic for one of the assessment periods). Because fatigue post-intervention is the most critical outcome assessment point, the 1st assessment (study entry) and the post-intervention assessment point at Week 10 after study entry will be required for inclusion in the hypothesis testing analysis. Randomly missing assessments at Week 10 will be handled within the statistical analysis described. Randomly missing item responses within study measures will be handled according to the instructions for each instrument when developed and validated. Missing data assessments and drop-out occurrences will be analyzed to inform future research. We do not expect those types of missing data to be random; therefore imputation procedures will not be conducted. Maximum Type I error of 0.05 (uncorrected and/or corrected as necessary) will be maintained for statistical significance and all analyses will be performed in consultation with Dr. Tooze.

Specific Aim 1. Key statistical tests will involve between group differences in mean values and group differences in the patterns (i.e., slopes) of individual changes from respective baseline values of the PROMIS fatigue and depressive symptoms scores. These tests will be evaluated using mixed-effects (or multilevel) generalized linear modeling procedures with robust variance estimation. Of particular relevance to this study, the flexibility of generalized linear modeling allows for analysis of not only univariate normal error distributions, but also multivariate dependent variable distributions and Poisson distributions. Because we expect there to be a correlation between fatigue and depressive symptoms, a multivariate approach will provide more unified (systemic) statistical tests of the intervention effects. These tests for specific effects on single outcome variables tend to be more powerful because standard errors are smaller. Our expectation is that there will be group differences in both the post-baseline means and shape (slope) of the outcome variable trajectories of participants

in the YST compared to the participants in the AC. Because of the presence of variables known to effect fatigue and depressive symptoms (e.g., use of methylphenidate), those variables will be adjusted for in the analysis (i.e., included as covariates). Analysis of differences in the intervention effect between gender and racial/ethnic subgroups will also be performed. Finally, in addition to statistical significance testing of the study and covariate effects in the models, bootstrapping methods will be used to generate 95% confidence intervals for all sample descriptive statistics and effect estimates. Changes in the proposed mediators will be summarized and analyzed using the same approach as described above. If changes in the proposed mediators are observed, exploratory longitudinal path analysis will be conducted to investigate the actual level of mediation apparent on fatigue and/or depressive symptoms. Further exploratory analyses will examine associations of the dose of the YST (i.e., days of in-person sessions completed plus days of home practice), outcome expectations and efficacy beliefs with fatigue, depressive symptoms, psychological stress/regulation of stress, circadian disruption, and inflammation.

Specific Aim 2. A critical element of this proposal is the inclusion of daily (vs. standard recalled) assessments of fatigue, depressive symptoms and proposed mediators, during two 2-week periods in the study (initial: 0-2 weeks, later: 8-10 weeks). Summaries of the proportion and frequency of missing daily assessments will inform the feasibility of collecting this type of data. Graphical displays of these daily reports will prove invaluable for informing both the patterns of the respective symptoms and mechanisms in and of themselves, and also for informing the optimal representation of the patterns in analyses with the recalled measures. Depending on missing data, study group differences in daily (or mean 2-day) values will be evaluated using mixed-effects generalized linear modeling. Findings and effect sizes garnered from these analyses will be compared to those resulting from recalled measures. Informed by the graphical displays, several summary indices of each of the two daily assessment periods (peak value, mean, coefficient of variation) will be generated for use in multi-method, multi-trait analyses of similarities and differences in the patterns of associations among the daily and recalled measures. This analysis will further inform which measures (and/or which summary indices) appear to be the best and most sensitive indices to use in future studies.

Specific Aim 3: Open-ended and interview data will be coded by the Qualitative Research Core led by Dr. Schlundt (Collaborator). Dr. Sohl will consult with the Core to develop a coding system and also code 10% of the responses to assess reliability. Coded responses will be interpreted with a thematic analysis.[105] The number of participants interviewed (20-40) will be decided by when thematic saturation is reached. Qualitative information gained will enrich quantitative results and inform the protocol of a larger trial.

10. DATA COLLECTION AND QUALITY ASSURANCE

10.1 Data Collection Forms

Questionnaires and blood draws will be collected by a blinded STM. Data records for each participant will be identified by a unique study code number that does not contain personal identifying information. Data collection forms which only have ID

numbers will be stored in a locking cabinet at CCC-WFU or in the PI's office building while on study at Wake Forest University. Data from these documents, clinical data from the medical chart and data collected via daily automated surveys will be entered into a REDCap database at Wake Forest University. The actigraphy data, audio recorded semi-structured interviews and videos of the intervention sessions will also only be coded by study ID number. Data collection forms are presented in the appendices as outlined in the Table of Contents.

All participants will be assigned a study ID number; however, it is necessary for the study team to know participants names during time on-study. Names will be maintained in a participant tracking database accessible only to approved study staff through password protected files stored on a secure server, not on laptops or thumb drives. To protect confidentiality, all data will be stored in a locked file cabinet located in the secured office of a STM or PI. All computers and data files will be password protected. All data processed will be in aggregate form and data collection forms will only be labeled with participant's unique identification number.

10.2 Data Management

The clinical site will not be responsible for data collection or management. Some data will be extracted from the medical record at the clinical site, though this data is part of routine monitoring and care of the patients.

CCC-WFU will serve as the data coordinating center. Data from Vanderbilt-Ingram Cancer center will be transferred securely to CCC-WFU utilizing Accelion.

Data collection forms are outlined in section 9.5 Outcomes and stored as summarized in the following table.

Summary of Data Storage

Informed consent document	Electronic Medical Record
Protocol registration form	ORIS
Study questionnaires (Weeks 0, 10, 14)	REDCap
Daily survey data	REDCap
Treatment fidelity data	REDCap
Clinical data	REDCap
Actigraphy data	Excel Files on Secure Server
Inflammation data	Excel Files on Secure Server
Adherence data	Excel Files on Secure Server
Qualitative data	Box hosted through Vanderbilt University and on Secure Server
Adverse events	ORIS

10.3 Quality Assurance

10.3.1 Training

All research staff will have completed the online Collaborative Institutional Training Initiative Training (CITI) prior to participation in research activities. Dr. Sohl will

directly oversee training of research staff in regards to conducting the planned research.

10.3.2 Quality Control Committee

The study team will generate Study Reports for the IMC and will provide information on the following study parameters: recruitment of subjects to the pilot study, adherence to the interventions, and adverse events that may be related to the interventions.

The frequency of review for this study differs according to the type of data and can be summarized in the following Table.

Frequency of data review

Data type	Frequency of review	Reviewer
Subject accrual (including compliance with protocol enrollment criteria)	Quarterly	PI, Independent Monitor(s)
Status of all enrolled subjects, as of date of reporting	Quarterly	PI, Independent Monitor(s)
Adherence data regarding study visits and intervention	Quarterly	PI, Independent Monitor(s)
AEs and rates	Quarterly	PI, Independent Monitor(s)
SAEs	Per occurrence	PI, Independent Monitor(s), IRB, NCCIH

10.3.3 Metrics

Review of the rate of subject accrual and compliance with inclusion/exclusion criteria will occur monthly by the PI during the first three months and then every quarter (4 months) to ensure that a sufficient number of participants are being enrolled and that they meet eligibility criteria and the targeted ethnic diversity goals outlined in the grant proposal (Targeted/Planned Enrollment Table).

Adherence of participants will be evaluated by documentation of participation in interventions during chemotherapy. We will consider high adherence to the intervention if subjects participate in 80% of the in-person interventions. If on review, adherence is below this threshold, Dr. Sohl will convene a conference call to discuss methods for improving adherence.

Dr. Sohl or study staff will also review all data collection forms on an ongoing basis (i.e., quarterly) for data completeness and accuracy as well as protocol compliance. A

study member not involved in data collection will enter the data. At least ten percent of all data entered from questionnaires will be randomly selected and verified for accuracy against original source documents. Any discrepancies will be discussed with the Independent Monitors. Data will also be reviewed for outliers and to determine if values are missing at random prior to analysis. Dr. Sohl will provide quarterly updates to the IMC and research mentors regarding patient accrual.

10.3.4 Protocol Deviations

Protocol deviations will be captured through direct observation by research staff regarding patient recruitment and enrollment, intervention administration, adherence, and safety monitoring. Protocol deviations will be reviewed by the principal investigator and discussed with research mentors and as needed with the IMC.

10.3.5 Monitoring

Dr. Sohl will monitor for protocol compliance, data quality, and review of documentation to assure protocol compliance. This will include review of informed consent process (upon enrollment), adverse event reporting (upon occurrence), and data collection (monthly).

11. PARTICIPANT RIGHTS AND CONFIDENTIALITY

11.1 Institutional Review Board (IRB) Review

This protocol and the informed consent document and any subsequent modifications will be reviewed and approved by the IRB or ethics committee responsible for oversight of the study.

11.2 Informed Consent Forms

Written informed consent will be obtained from each subject at entry into the study. Informed consent is obtained by the following process:

1. The patient will be asked to review the study consent form.
2. The PI or STM will meet with the patient either in person or by telephone to review the form, to confirm the patient understands the study, and to answer any questions that the patient might have.
3. Once the patient demonstrates understanding of the study and agrees to participate in the study, the consent will be signed remotely or in person. If signed remotely, patients will be asked to send the form back to us by a secure means, as well as bring the original with them to their next clinic visit.

A copy of the consent form will be given to the participant the next time they are in clinic, and the original copy will be kept in the participant's file. Patients who cannot consent for themselves in English will not be eligible to participate.

11.3 Participant Confidentiality

Any data, specimens, forms, reports, video recordings, and other records that leave the site will be identified only by a participant identification number (Participant ID, PID) to maintain confidentiality. All records will be kept in a locked file cabinet. All computer entry and networking programs will be done using PIDs only. Information will not be released without written permission of the participant, except as necessary for monitoring by the IRB and the NCCIH.

11.4 Study Discontinuation

The study may be discontinued at any time by the IRB, the NCCIH, or other government agencies as part of their duties to ensure that research participants are protected.

12. COMMITTEES

The Independent Monitoring Committee (IMC) for this study is comprised of members of the Wake Forest School of Medicine's Institutional Data and Safety Monitoring Board who are not associated with this research project and thus work independently of the PI, Dr. Stephanie Sohl. They are not part of the key personnel involved in this grant. They are qualified to review the patient safety data generated by this study because of their respective unique expertise in the areas of oncology, mental health/ethics and statistics.

13. PUBLICATION OF RESEARCH FINDINGS

Any presentation, abstract, or manuscript will be made available for review by the sponsor and the NCCIH prior to submission.

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15. SUPPLEMENTS/APPENDICES

15.2.1 Appendix A: Informed Consent Documents and Form for Documentation


01716 Consent 6-17-16.pdf


01716_Documenting _the_Consent_Proces

15.2.2 Appendix B: Yoga Skills Training Home Practice Guide


YSTHomePracticeGuide.docx

15.2.3 Appendix C: Yoga Skills Training Home Diary


YSTHomeDiary.docx

15.2.4 Appendix D: Attention Control Home Diary


HomeDiaryForms.docx

15.2.5 Appendix E: Treatment Fidelity Forms


FidelityCheckAC.docx


FidelityCheckYST.doc

15.2.6 Appendix F: Chart Review Form and Questionnaires


Pro-You_ChartReview.docx


Questionnaire 1.pdf


Questionnaire 2.pdf


Questionnaire 3.pdf


Questionnaire 4.pdf

15.3.7 Appendix G: Semi-Structured Interview Guide


Semi-structuredInterviewGuide_AC.docx


Semi-structuredInterviewGuide_YST.docx

15.3.8 Appendix H: Daily Survey

DailyMeasuresforParticipants.doc

15.2.9 Appendix I: Recruitment Script

RecruitmentSCRIPT.docx

15.2.10 Appendix J: Recruitment Flyer

RecruitmentFlyer.docx

15.2.11 Appendix K: Eligibility Checklist

Appendix_EligibilityChecklist.docx

15.2.12 Appendix L: Enrollment Form

01716 Protocol Registration.docx

15.2.13 Appendix M: Thank You Letter

ThankYouLetter.docx

15.2.14 Appendix N: Adverse Events Reporting Form

Serious_Adverse_Events_Form_ver_3.pdf