CCCWFU 97218: Support for Optimal Recovery following Gynecologic Surgery Study (SOARING)

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PRÉCIS

Study Title

Support for **O**ptim**a**l **R**ecovery follow**in**g **G**ynecologic Surgery Study **(SOARING)**

Objectives

The overall aims of the study are to determine feasibility, any adverse events, variability of proposed outcomes, and acceptability of the Mindful Movement and Breathing (eMMB) and Attention Control (AC) interventions that have been adapted to the eHealth Format. To accomplish these aims, we will conduct a pilot randomized controlled trial of the eMMB compared to AC among 31 women undergoing surgery for a suspected gynecologic malignancy. More specifically, we will:

(1) Calculate recruitment, adherence, assessment completion, and retention rates;

(2) Document the frequency of adverse events;

(3) Assess descriptive data on proposed outcomes (i.e., pain, sleep disturbances, psychological distress) for the next phase of study; and

(3) Qualitatively assess acceptability to guide future study planning.

Design and Outcomes

We propose a prospective stratified randomized controlled pilot study investigating the feasibility of comparing the eMMB to AC for improving pain, sleep disturbances, and psychological stress. Participants enrolled (N=31) will be randomized 1:1: to eMMB or AC. Allocation will be stratified by cancer type (i.e. ovarian, uterine) and invasiveness of the planned surgical procedure type (i.e., laparotomy or robotic). Patient-reported assessments will be conducted at four time points: before surgery (baseline), one day after surgery, two weeks after surgery and 4 weeks after surgery. Participants will also be asked to complete daily assessments of outcomes and adherence to home practice of the intervention and wear a wrist actigraphy device for one week before and one week following surgery. In addition, medical records will be reviewed, treatment fidelity observed, and an interview conducted at a follow-up clinic visit or by telephone. We will also track recruitment, adherence to the videoconference intervention, any other contact with interventionists, adverse events, and completion of assessments. Those who decline participation or drop out of the study will be asked for feedback about their choices. Our findings will inform an efficacy trial of the eMMB for improving surgical outcomes of adults who undergo surgery for a suspected gynecologic malignancy.

Interventions and Duration

In-person MMB and AC interventions investigated in our Preliminary Research have been adapted to be implemented by eHealth. The initial dose of the eMMB and AC interventions will include a call to invite participants to initiate additional guidance upon request prior to surgery and a meeting with the participantby videoconferencing the day following surgery. Participants will also be given a self-directed video to be used before surgery and daily for two weeks following surgery in the eMMB group

and diaries to complete daily in the AC group.

The approximately 20-minute eMMB will teach: (a) Awareness Meditation - noticing the current state of the body, emotions, thoughts, energy, and breath; (b) Movement – gentle movements coordinated with the breath; (c) Breathing and Relaxation - placing the hands above the navel and noticing them rise and fall with a focus on slightly extending the exhale; (d) Awareness Meditation – 5 minutes of awareness of noticing the natural breath without changing it to enhance mindfulness. The intention to maintain attention or mindfulness (sthira), comfort and ease (sukha) is highlighted throughout the eMMB.

An AC group focused on providing caring attention will be employed to account for the added time, attention, interaction with an interventionist, and efficacy expectations of the eMMB. In addition, the interventionist will ask patients to write brief diary entries daily at home as used in previous research and our current study. The AC will be implemented by an individual with experience working in a medical setting who will be trained to create and maintain a relationship by using techniques such as active listening, reflection of statements, and avoiding negative judgments.

Sample Size and Population

The target population of the proposed research is adult women scheduled to undergo surgery for a suspected gynecologic malignancy at the Wake Forest Baptist Comprehensive Cancer Center (WFBCCC). We will enroll 31 participants, who will be eligible regardless of race, ethnicity, or national origin.

1. STUDY OBJECTIVES

1.1 Primary Objective

The overall aims of the study are to determine feasibility, any adverse events, variability of proposed outcomes and acceptability of the Mindful Movement and Breathing (eMMB) and Attention Control (AC) interventions that have been adapted to the eHealth Format. To accomplish these aims, we will conduct a pilot randomized controlled trial to of the eMMB compared to AC among 31 women undergoing surgery for a suspected gynecologic malignancy. More specifically, the primary feasibility objective is to:

(1) Calculate recruitment, adherence, assessment completion, and retention rates;

Hypothesis: We hypothesize that we will enroll at least 50% of eligible patients, participants will adhere to 70% of the interventions, and at least 70% of participants will complete study assessments and be retained in the study.

An adequate retention rate at week 2 (future primary outcome assessment time point) will be our primary indicator that this study was successful.

1.2 Secondary Objectives

(2) Document the frequency of adverse events;

(3) Assess descriptive data on proposed outcomes (i.e., pain, sleep disturbances, psychological distress) for the next phase of study; and

(4) Qualitatively assess acceptability to guide future study planning. Refining study methodology will result in a Manual of Operations and Procedures for an efficacy trial.

2. BACKGROUND AND RATIONALE

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

Improved management of acute perioperative pain and co-morbid symptoms may proactively reach an at-risk population and reduce the burden of chronic pain. Over 80,000 women diagnosed with gynecologic cancers each year regularly face major abdominal surgery.[1] Most (64%) experience considerable pain,[2] yet management of postoperative pain is still inadequate.[3] For example, less than half of patients who underwent surgery for cancer felt their postsurgical pain was relieved by 50% (on scale from 0-100%).[9] In addition, many of these women also report postoperative sleep disturbances (39-70%),[2,4] and psychological distress (20%),[2,5] both associated with pain.[2,6–8] There are likely bidirectional relationships among pain, sleep disturbances and psychological distress.[4] Such acute postoperative symptoms are important to address, because they predict persistent symptoms[4,9,10] and a reduced quality of life.[11,12] Therefore, interventions to simultaneously improve perioperative pain, sleep disturbances, and psychological distress are needed to impact immediate and longer-term outcomes including preventing the transition of acute to chronic pain.[13]

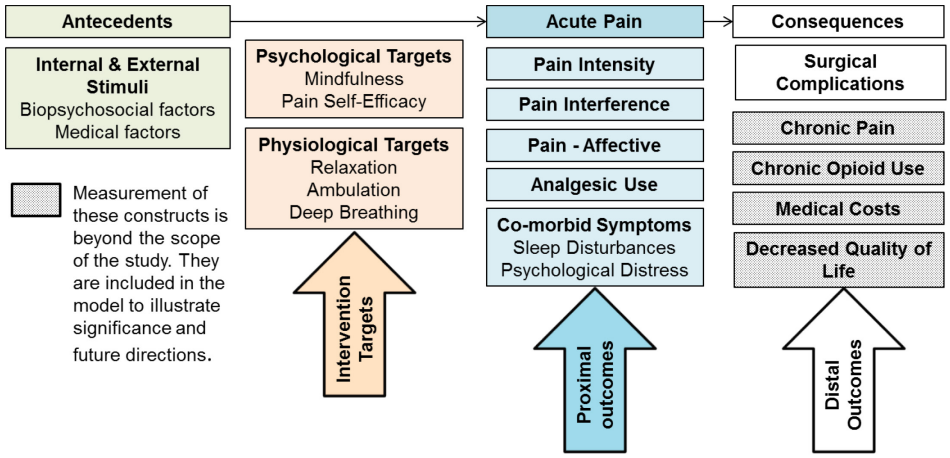
Predictors of chronic pain include the efficacy of initial pain treatment.[14] Furthermore, those who are women, have surgery and are diagnosed with cancer are most vulnerable to chronic pain.[13] Even post-treatment, the prevalence of chronic pain is estimated to be up to 40% among post-treatment cancer survivors[15] and women with cancer report more severe pain than do men.[16] Due to the increasing numbers of patients surviving cancer for longer periods of time, pain management is a chronic problem with guidelines for treatment similar to treatment of chronic pain in the general population.[17] These guidelines recommend use of multimodal therapies with a stated preference for nonpharmacologic therapy (including mind-body techniques such as mindfulness and relaxation) and nonopioid pharmacologic therapy.[14,18] However, the level of evidence for use of such modalities is only moderate.[14,19] Additional fully-powered randomized controlled trials of nonpharmacological interventions compared to active control groups are needed. Similarly, adverse effects of long-term opioid use and potential abuse among cancer survivors contributes to the concern of the larger national opioid epidemic.[17,20,21] Indeed, one study reported that 29% of cancer patients were at high risk for opioid misuse[21] and women respond differently to pain medication such that they use more postsurgical opioid medication and may be more susceptible to addiction.[13,22] Thus, preventing the transition of acute to chronic pain and reducing related opioid use in the proposed high risk population would have a substantial public health impact.[13,20]

Yoga is a multimodal intervention that may optimally address pain and co-morbid symptoms. Clinical guidelines for postoperative pain management recommend including nonpharmacological interventions and pain medication since they may have an additive effect on pain relief.[19] Pain has sensory (e.g., location, physical characteristics) and affective dimensions (e.g., unpleasantness, appraisal of consequences); interventions to alleviate both may be more effective than those that address only the sensory aspects of pain.[23,24] Mind-body interventions, are commonly sought after nonpharmacological approaches for addressing pain, sleep disturbances, and psychological stress, particularly in cancer patients.[13,25,26] Specifically, yoga is gaining popularity,[27] and there is a generally positive impression of and curiosity about yoga.[28] Yoga is a promising intervention to simultaneously improve such aspects of pain, and associated symptoms (i.e., sleep disturbances, psychological distress). The key elements of yoga are movements, breathing exercises, and meditation.[29] Empirical evidence supports the efficacy of yoga as an intervention for reducing pain,[30–32] sleep disturbances,[33] and psychological distress,[34,35] in a variety of populations[36] and in studies specific to cancer survivors.[37–39] There is some evidences for the benefit of yoga in a surgical context. In one study, yoga taught to women undergoing surgery for suspected breast cancer reduced length of hospital stay and improved wound healing.[40] These results support the possible efficacy of yoga for reducing postoperative complications. However, that study did not assess the effect of yoga on pain. Overall, evidence supporting the efficacy of yoga for psychological distress is strong when implemented as group classes for women with breast cancer and less certain regarding the efficacy for sleep disturbances and pain. The evidence supporting the efficacy of yoga for pain primarily consists of pilot studies in women

with breast cancer or studies of yoga for low back pain.[30,41] There are limited studies investigating the efficacy of yoga for other cancer types or perioperatively.

Yoga has a potential advantage over other perioperative interventions (i.e., relaxation, hypnosis)[32,42] because it has multiple components that also support the goals of usual care (e.g., to encourage early postoperative ambulation and deep breathing via incentive spirometry) and thus may help treat other surgical comlications.[43–45] Usual care to manage pain includes teaching patients to splint the abdomen by holding a pillow to it before coughing or deep breaths, allowing them to perform these functions with less pain and monitoring pain every four hours on a scale from 0-10 (10 for the worst pain) to ensure that adequate pain medication is given. Early postoperative ambulation aims to reduce postoperative ileus (bowel obstruction) and deep venous thrombosis (blood clots). Deep breathing via incentive spirometry encourages patients to clear the lungs of fluid to prevent pneumonia. About 30% of women undergoing surgery for a suspected gynecologic malignancy have a surgical complication (e.g., postoperative ileus, deep venous thrombosis, pneumonia);[46,47] these contribute substantially to costs.[8,46] Research supports that yoga breathing practices improve lung function[36,48] and yoga movements increase mobility (i.e., balance and flexibility).[36] Further, combining awareness with movement is a method of promoting meditation that may be easier for some people to experience than methods that are taught while still.[49] Thus, adding yoga to usual care may be helpful for postsurgical pain in a number of ways.

Proposed mechanisms of effects of yoga on pain and co-morbid symptoms. A Self-Regulation Framework[50,51] proposes both psychological (e.g., mindfulness, self-efficacy) and physiological (e.g., relaxation, ambulation, deep breathing) explanations for the positive influence of yoga, which primarily affects psychological and physical well-being through reducing the stress response. One component of the Self-Regulation Framework proposes that cognitive appraisals such as self-efficacy for managing pain[30,52,53] could explain the proposed impact of learning self-regulation skills (i.e., yoga) on pain. A recent study also suggested that mind-body interventions likely address pain through a mechanism different than opioid medication, potentially providing a self-regulation strategy that works with medication in an additive fashion to improve pain management.[54] Thus, mind-body interventions may further enhance pain control for those taking medications, and potentially reduce the risk of postoperative chronic pain and possible opioid addiction by empowering patients to use other pain-reducing strategies. The conceptual framework highlighting constructs considered in the current study informed by this prior work is presented in **Figure 1**.[50,51,54]



Implementation of yoga as a self-directed eHealth intervention may increase adherence and aid dissemination, which will lead to a greater public health impact. A growing body of literatures supports the idea that behavioral skills can be taught through information technology (eHealth).[55] However, few eHealth interventions have been quantitatively evaluated specifically for people with cancer; thus their efficacy for cancer patients is unclear.[56,57] To improve upon limitations of current research, future studies should incorporate clinically meaningful validated measures and utilize a conceptual framework to improve methodological rigor. Implementing behavioral interventions via eHealth could address the unmet psychosocial needs of cancer patients in a way that reduces costs and thus could have public health impact.[56] EHealth addresses barriers to participation such as accessibility (e.g., one treatment can be utilized by many people simultaneously), travel distance, and dissemination (e.g., increased treatment fidelity).[56]

Some research supports that adherence to treatment offered through behavioral internet interventions (e.g., for improving depression, physical activity) is as good as adherence to face-to face interventions.[58,59] However, eHealth interventions have different levels of human interaction from exclusively self-directed to requiring considerable content guidance from a human provider.[56] The Supportive Accountability[60] model provides a framework for assessing how supportive interactions may influence intervention adherence. This theory posits that interaction factors, such as accountability, bond, and legitimacy, can potentially influence adherence to internet interventions with bond being the most important when the treatment focus is on providing skills training.[60] In addition, the Supportive Accountability model suggests that the influence of these interaction factors on adherence may be moderated by motivation and communication "bandwidth" (i.e., the number of communication cues a medium can convey). Although some suppose that as the bandwidth lessens, the quality of interaction factors lessens, this is not always so, people can effectively communicate through various media. Thus, the optimal level of content guidance and communication medium to implement behavioral interventions is yet to be determined.[56,60]

2.2 Study Rationale

The proposed Mindful Movement and Breathing (eMMB) intervention adapts key elements of a longer intervention (about 10 weeks[61]) to a shorter format. Yoga implemented as traditional (often longer) group classes has demonstrated efficacy for reducing pain,[31,38] sleep disturbances,[33] and psychological distress.[34,35,61] Other researchers, and our team have shown that interventions to reduce pain, sleep disturbances and psychological distress such as cognitive-behavioral therapy, Mindfulness-based Stress Reduction (Co-I Zeidan), and yoga (PI: Sohl) can be successfully adapted to be brief.[62–65] Such interventions can provide more immediate benefit and thus enhance participation and adherence. In fact, beneficial psychological and physiological effects were found after 15-minutes of yoga in healthy adults, with data suggesting more sustained improvement in respiration rate in the yoga group vs. meditation.[49] The eMMB teaches essential aspects of yoga from the same tradition as implemented with other cancer survivors by Dr. Danhauer (Co-Investigator)[61] in a manner that may be easily adapted to other perioperative and cancer populations. This approach aims to design an intervention with promise for future dissemination.[66]

The proposed Mindful Movement and Breathing (eMMB) intervention is implemented perioperatively. Although other yoga studies have been implemented in clinical settings, these studies either did not exclusively evaluate yoga[67] or the yoga interventions were not brief.[40,68] The eMMB is designed to improve upon previous interventions with its brevity and its adaptation to the acute needs of patients undergoing surgery for cancer. In addition, the eMMB will potentially contribute to a shift in the paradigm of yoga, which has been typically implemented in the United States as a complementary medicine modality (a separate practice used together with usual care), to become a component of integrative medicine (incorporated into usual care in a coordinated way).[69]

Interest in perioperative yoga (PI: Sohl, Co-I's: Danhauer & Tooze). To investigate patient interest in our proposed study, we surveyed 9 women who were in-hospital before or after surgery for suspected gynecologic malignancy.[70] Of 20 women approached, 10 (mean age = 51 years; 89% White) agreed to complete the survey. Reasons that women declined participation included: not interested (n=8); non-cancer related health issues (n=1); other (n=1); plus one screen failure. Participants indicated on a scale from 1 (not useful) to 10 (useful) that they expected that the described "Yoga Skills Training" (YST) would be useful for reducing pain (M=6.7; SD=2.5) and distress (M=6.9; SD=2.0). They also provided feedback on the intervention name including that the word 'yoga' might deter some potential participants. The average length of time women reported being willing to participate in a YST session was 23 minutes. All participants indicated that they would be interested in learning the YST on their own and video was the most popular format selected for independent practice (n=4), followed by CD (n=2), written material (n=1) and other (n=2). Thus, the proposed intervention is called "Mindful Movement and Breathing" and will primarily be implemented via a 20-minute video.

Perioperative yoga feasibility (PI: Sohl, Co-I's: Danhauer & Tooze). "Mindful Movement and Breathing (MMB)" describes the gentle physical activity in this intervention compared to other types of yoga. The MMB was designed for patients receiving chemotherapy[71] and then tested in this non-randomized trial to determine feasibility of the MMB (three 20-minute in person sessions) among women undergoing an exploratory laparotomy for a suspected gynecologic malignancy (60% ovarian; 20% uterine; 20% cervical).[65] Type of surgery was the primary reason for exclusion (86%) since we did not include less invasive surgeries (e.g., robotic). Of 18 eligible women approached, 10 (age M = 54.7 years; 90% White) enrolled in the study (55% recruitment). Seven women were retained in the study and no adverse events were reported. Only five women received the MMB pre-operatively due to scheduling challenges. Participants completed two Visual Analogue Scale items of pain and distress immediately before and after each MMB (average session = 20.6 minutes). Pain and distress decreased with moderate to large effects (Table 1). On a scale from 1 (not at all) to 5 (very much) patients liked the MMB (M = 4.29, SD = 0.76), found it helpful (M = 3.71, SD = 0.95), and planned to continue to use what they learned (M = 3.71, SD = 1.11). These data support feasibility of testing the MMB in these patients, but revealed challenges to consistent implementation of the in-person MMB before surgery. Therefore, the proposed intervention will utilize an eHealth approach to test whether adherence would be greater. In addition, the proposed study will also include women scheduled for less invasive types of gynecologic cancer surgeries, which have become more common and may have more room for improvement in pain management.

Table 1. Pilot Results of MMB Before and After Surgery

	Before (n=5)	Day 1 After (n=7)	Day 2 After (n=7)
Pain	d = -0.67	d = -0.76	d = -0.95
Distress	d = -0.76	d = -0.66	d = -1.08

Strategies for disseminating yoga (PI: Danhauer). Two other prior pilot studies of gentle yoga for women with cancer conducted by our team demonstrated that group yoga classes reduced fatigue, depressive symptoms, and sleep disturbances.[61,72] We next conducted a 3-site feasibility study through the Wake Forest NCI Community Oncology Research Program (NCORP) Research Base of women undergoing chemotherapy treatment for breast cancer (N=40) to investigate the feasibility of more broadly implementing this promising intervention *(Co-I: Sohl)*. The primary difficulty was the need for specially trained teachers at each site.[73] We then piloted yoga classes using videoconferencing, which allowed participants (N=5) to take part in study classes from a convenient location and two-way interaction with instructors and other participants. Twelve, 75-minute cancer-adapted Integral Yoga classes were offered twice weekly during the 6-week course of radiation therapy. Participants suggested that simplifying the technology would have increased their participation or otherwise improved their experience; however, participants did like the staying at home for the interventions. Participants also wanted more variety in the schedule and shorter classes. The proposed research will utilize videoconferencing only when participants have assistance from research staff. Home practice sessions will be shorter (20-minutes) and implemented via simpler technology. Future directions for

the proposed research will employ Dr. Danhauer's experience with NCORP (U10CA081851)**.**

Efficacy of a brief mind-body intervention for reducing pain (PI: Zeidan). A brief mindfulness meditation intervention (four 20-minute training sessions) was significantly more effective at reducing pain than two well-validated placebo interventions (placebo cream, sham mindfulness mediation).[74] Yet, all had significantly reduced pain intensity and unpleasantness ratings compared to the control group (reading). Sham mindfulness meditation (participants trained to take deep breaths and led to believe they were practicing mindfulness) was associated with greater reductions in respiration rate, demonstrating a mechanistic difference between sham and mindfulness meditation. Mindfulness meditation–related pain relief was associated with greater psychological executive-level modulation of pain and, in contrast, sham mindfulness meditation–induced analgesia was driven by physiological processes consistent with placebo and relaxation. Similar instructions for nonjudgmental attention to the breath, and instructions for taking deep breaths to slow breathing, will be incorporated into the eMMB to optimize the influence of the intervention on pain reduction.

3. STUDY DESIGN

The proposed research will determine feasibility and acceptability of investigating the eMMB and AC interventions to reduce pain and other surgical outcomes through an exploratory stratified randomized controlled pilot study among 31 women undergoing surgery for suspected gynecologic malignancies.

Participants enrolled will be randomized 1:1 to eMMB or AC. Allocation will stratified by cancer type (i.e., ovarian or uterine) and invasiveness of the planned surgical procedure type (i.e., laparotomy or robotic). Patient-reported assessments will be conducted at four time points: before surgery (baseline), one day after surgery, two weeks after surgery and 4 weeks after surgery. Participants will also be asked to complete daily assessments of outcomes and adherence to home practice of the intervention and wear a wrist actigraphy device for up to one week before and one week following surgery. In addition, medical records will be reviewed, treatment fidelity observed, and an interview conducted at a follow-up clinic visit or by telephone. We will also track recruitment, adherence to the videoconference intervention, any other contact with interventionists, and completion of assessments. Our findings will inform an efficacy trial of the eMMB for improving surgical outcomes of adults who undergo surgery for a suspected gynecologic malignancy.

In-person MMB and AC interventions investigated in our Preliminary Research will be adapted in the proposed research to be implemented by eHealth. The initial dose of the eMMB and AC interventions will include a call to invite participants to initiate additional guidance upon request prior to surgery and a meeting with the participant via videoconferencing the day following surgery. Participants will also be given a self-directed video to be used before surgery and daily for two weeks following surgery in the eMMB group and diaries to complete daily in the AC group.

The approximately 20-minute eMMB will teach: (a) Awareness Meditation - noticing the current state of the body, emotions, thoughts, energy, and breath; (b) Movement – gentle movements coordinated with the breath; (c) Breathing and Relaxation - placing the hands above the navel and noticing them rise and fall with a focus on slightly extending the exhale; (d) Awareness Meditation – 5 minutes of awareness of noticing the natural breath without changing it to enhance mindfulness. The intention to maintain attention or mindfulness (sthira), comfort and ease (sukha) is highlighted throughout the eMMB.

An AC group focused on providing caring attention will be employed to account for the added time, attention, interaction with an interventionist, and efficacy expectations of the eMMB. In addition, the interventionist will ask patients to write brief diary entries daily at home as used in previous research and our current study. The AC will be implemented by an individual with experience working in a medical setting who will be trained to create and maintain a relationship by using techniques such as active listening, reflection of statements, and avoiding negative judgments.

The total length of time each participant will be on study is approximately 4 weeks. The enrollment period for the trial is expected to continue for 12 months.

4. SELECTION AND ENROLLMENT OF PARTICIPANTS

We will seek approval from the Institutional Review Board (IRB) prior to implementing the proposed study and take precautions to ensure adequate protection of human subjects. Recruitment of women scheduled to undergo surgery for a suspected gynecologic malignancy at the Wake Forest Baptist Comprehensive Cancer Center (WFBCCC) will be facilitated by Dr. Kelly (Co-Investigator). To increase homogeneity, only the most prevalent gynecologic malignancies will be recruited (i.e. uterine, ovarian) that occur in only women. We chose this target population because adult women undergoing surgery for suspected cancer are at particularly high risk for experiencing chronic pain.[13] In addition, this sample reduces variability due to sex differences in pain tolerance[75] and response to pain medication.[13] There are multiple theories that may explain these differences. Of particular note is the "vulnerability theory", which posits that sex hormones affect the nervous system's and psychological responses to pain.[13]

4.1 Inclusion Criteria

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

- Adult females (≥18 years of age)
- Scheduled for an abdominal gynecological surgery (i.e. uterine, ovarian) to remove a suspected malignancy
- Have an Eastern Cooperative Oncology Group (ECOG) performance status of ≤1
- Cognitively able to complete assessments as judged by the study team
- Able to understand, read and write English.

4.2 Exclusion Criteria

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

- Have schizophrenia or any other psychotic disorder;
- Have a diagnosed sleep disorder including untreated obstructive sleep apnea, periodic limb movement disorder, or restless leg syndrome.

4.3 Study Enrollment Procedures

Individuals scheduled to undergo surgery for suspected gynecologic malignancies (i.e., uterine, ovarian) will be recruited from the Wake Forest Baptist Comprehensive Cancer Center (WFBCCC). To identify potential patients, the Project Manager will screen appointment lists and communicate with attending physicians regarding patients' potential eligibility for the 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 and referred by the physician, the Project Manager will approach or call interested patients prior to surgery to explain the protocol, answer questions, 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 electronically or in person. If signed electronically, patients will be asked to send the form back to us by a secure means (e.g., REDCap). In the case that the patient is consented electronically, either a hard copy or email attachment of the informed consent document will be provided to the participant. (Appendix A: Informed Consent Document). The original copy will be kept in the participant's file. Each participant will be asked to separately agree to be audio recorded for the study, which will not affect their ability to participate. If they do consent to be videotaped, they are told in the consent form that they can ask not to be included in the filming or withdraw their consent to be videotaped at any time. These videos are focused on the interventionist for the sole purpose of increasing treatment fidelity.

Eligible participants enrolled in the study will be randomized after baseline assessments to the eMMB or AC prior to surgery.

Randomization. Participants enrolled will be randomized 1:1 to eMMB or AC. Allocation will be computer-generated, stratified by cancer type (i.e. ovarian, uterine), and concealed by Dr. Tooze (Biostatistician). Study team members will not know group assignment when enrolling participants. The Project Manager and PI who assign participants to interventions will be made aware of group assignment after a participant has provided informed consent. The Clinical Studies Staff member who will collect primary outcome data will be blinded to group assignment. Participants will be informed that they could be randomly assigned to 1 of 2 different supportive treatments with a general description of what they will involve (i.e., counseling,

gentle movement, writing, and/or relaxation strategies) and will be asked not to discuss study procedures with their treating surgeon, medical staff, or research personnel. Thus, participants and healthcare providers will also be blinded to randomization.

5. STUDY INTERVENTIONS

5.1 Interventions, Administration, and Duration

Active Intervention. The Mindful Movement and Breathing (eMMB) intervention will be administered individually via telephone and video conference for initial guidance and is primarily intended to be self-directed (video). We considered the style, delivery, components of the intervention, specific class sequences, facilitation of home practice, dose, dealing with modifications, selection of instructors, and measurement of intervention fidelity, as recommended in the development of a yoga intervention for a randomized trial.[76]

Style. The content of the eMMB was informed by the PI's training from the Integral Yoga Academy's Yoga for People with Cancer Teacher Training and Urban Zen Integrative Therapy training, and was refined for this study by consulting with expert yoga therapists from the Krishnamacharya tradition (led by Dr. Wheeler, Consultant) and an expert in instructing mindfulness for reducing pain (Dr. Zeidan, Co-Investigator). Expert yoga therapists from the Krishnamacharya tradition are ideal for informing this approach since this tradition systematically selects yoga practices based on therapeutic targets (e.g., pain) and places an emphasis on daily home practice.[77,78] Furthermore, the eMMB aims to promote mindfulness and relaxation.

Delivery components and class sequence. The approximately 20-minute eMMB will teach: (a) Awareness Meditation - 2 minutes of noticing the current state of the body, emotions, thoughts, energy, and breath. Brief meditation has been shown to be effective for decreasing pain,[79] sleep disturbance[80] and psychological distress[81] and will increase mindfulness to facilitate safe physical movements; (b) Movement – 10 minutes of gentle movements coordinated with the breath also aim to enhance mindfulness to reduce pain, facilitate bowel movement (to prevent ileus) and blood flow (to prevent deep venous thrombosis); (c) Breathing and Relaxation - 3 minutes of placing the hands above the navel (rather than on the belly to avoid discomfort) and noticing them rise and fall with a focus on slightly extending the exhale to induce relaxation. This practice aims to improve lung capacity (to reduce pulmonary compromise) and reduce pain, sleep disturbance and psychological distress; (d) Awareness Meditation – 5 minutes of awareness of noticing the natural breath without changing it to enhance mindfulness. The intention to maintain attention or mindfulness (*sthira*), comfort and ease (*sukha)* is highlighted throughout the eMMB. We also propose that teaching these skills will increase self-efficacy for pain management through providing successful pain management experiences.

Dealing with modifications. The movements were chosen to be appropriate following surgery. Each session contains the same content, but the number of repetitions and the magnitude of movements are self-adapted based on how the participant is feeling. Any medical restrictions are within the scope of the eMMB.

Selection of instructors. Yoga instructors (one primary, two back-ups) will be contracted employees, accredited (i.e., certified as at least 200-hour-level teachers with the Yoga Alliance), and experienced teaching patients with medical conditions.

Dose and Implementation of eMMB. A 20-minute eMMB video will be saved as a local file on study tablets and/or will be accessible via the internet (participants will be given the option to receive a link to the study video via email). Participants will also be given a written description of the eMMB practice. Although guidance (i.e., supportive accountability[60]) is important in promoting adherence to eHealth interventions, one study of a stress-management intervention found that adherence-focused guidance (e.g., email reminders, guidance upon request by participants) was as good as more resource intensive content-focused guidance.[82] Thus, in the proposed study, participants will be given the video before surgery and asked to watch it at least once before the procedure. The yoga instructor will call participants before surgery to initiate additional guidance upon request at any time throughout the study and meet with the participant via videoconferencing using Cisco WebEx in the privacy of the hospital room the day following surgery (postoperative day 1 or as soon as feasible). Cisco WebEx supports compliance with the administrative and physical safeguards sections of the final HIPAA Security Rules.[83] The yoga instructors' contact information will be provided with the intervention materials indicating their hours of availability and expected response time. Instructors will attempt to call participants 2 times prior to surgery without leaving a message. Participants will be given an option to communicate with instructors via text messaging from a Medical Center device to increase convenience of scheduling. Meeting live via videoconference will allow yoga instructors to see participants and ensure that they feel comfortable completing the movements postoperatively. The videoconferencing session will be facilitated by the Project Manager and will be audio recorded. If problems transmitting the live intervention occur or it is not possible to complete the intervention in the clinical setting, we will have the interventionist lead the intervention and answer questions by telephone. Participants will be asked to continue to use the video daily for two weeks following surgery and as long as they choose thereafter. The Project Manager will monitor patient-reported self-directed use of the video and call to check in with all participants after the first two days. This dose of content-focused guidance is similar to that found to be effective in other brief or primarily self-directed interventions.[84,85] For example, hypnosis implemented during one 15-minute pre-operative in-person session, with instructions for how patients could use hypnosis on their own, reduced postoperative pain in women undergoing breast cancer surgery.[84] A self-directed approach may also empower participants to establish self-regulation strategies.

Attention Control (AC). An AC group focused on providing caring attention will be employed to account for the added time, attention, interaction with an interventionist, and efficacy expectations of the eMMB as recommended for the study of mind-body practices[86] and used in previous studies.[84,87,88] In addition, the interventionist will ask patients to write brief diary entries once before surgery and daily for two weeks following surgery. A diary form will be saved as a local file on study tablets via the

REDCap App and/or will be accessible via the internet (participants will be given the option to receive a link to the study diary via email). Participants will also be given the option to complete a paper diary. The Project Manager will monitor patient-reported self-directed diary completion and call to check in with participants if they have not completed the diary after the first two days. The AC will not include instruction of movement, meditation or breathing practices, which are the active ingredients of the eMMB. The format for interactions with a professional, amount of recommended home practice, and home assessments will be matched to the eMMB. The AC interventionist will call participants before surgery to initiate additional caring attention upon request at any time throughout the study and meet with the participant via videoconferencing following surgery (postoperative day 1 or as soon as feasible) for 30 minutes to provide caring attention. The videoconferencing session will be facilitated by the Project Manager and will be recorded. The AC will be implemented by an individual with experience working in a medical setting who will be trained to create and maintain a relationship by using techniques such as active listening, reflection of statements, and avoiding negative judgments. S(he) will utilize standardized instructions to prompt the patient as adapted from previous studies[87,89,90]: "*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*."[90]

5.2 Handling of Study Interventions

Participants will be informed that they could be randomly assigned to 1 of 2 different supportive treatments with a general description of what they will involve (i.e., counseling, gentle movement, writing, and/or relaxation strategies). Information about both arms will be revealed to participants after completion of data collection.

Measurement of intervention fidelity. Recommended steps will be taken to ensure treatment fidelity of the videoconference session for both groups to increase reproduceability.[91,92] The PI and expert yoga therapist (Wheeler) will train the interventionists to guide participants on the eMMB. The PI and Dr. Danhauer will train the interventionists on the AC. All sessions will be recorded and 20% randomly selected for review by Dr. Wheeler (eMMB) or Dr. Danhauer (AC). Further, the interventionists and Dr. Wheeler or Dr. Danhauer will meet monthly by phone to support them in maintaining familiarity with the protocol.

5.3 Concomitant Interventions

5.3.1 Allowed Interventions

All participants will continue with routine treatment of medical conditions including 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) Completion of the videoconference session; (2) any additional contact with the interventionists; (3) use of the self-directed intervention: measured daily for up to one week before and one week after surgery as assessed in another yoga study[38] and self-reported retrospectively (in the past week) at postoperative weeks 2 and 4. Instructors will directly observe and document adherence to the videoconference session. We will consider adequate adherence to protocol if 70% participants complete the planned video conferencing session one day of home practice before and 3 or more days of home practice per week for the two weeks following surgery.

6. STUDY PROCEDURES

6.1 Schedule of Evaluations

Assessment	Screening: (Day-14 to Day -1)	Baseline, Enrollment, Randomization: (Day 0)	Week 0	AC or eMMB (Day1)	Week1	Week 2	Follow-up (Week 4)
Inclusion/Exclusion Criteria	X						
Communication with Provider	X						
Informed Consent Form		X					
Enrollment/Randomization		X					
Demographics		X					
Clinical Data		X					X
Questionnaire		X		X		X	X
Daily Survey			X		X		
Actigraphy			X		X		
Treatment Fidelity				X			
Intervention Home Practice			X		X	X	X
Adherence				X			
Interventionist Communication			X		X		
Adverse Events				X		X	X
Interview							X

Note. *AC = Attention Control; eMMB = EMindful Movement and Breathing*

6.2 Description of Evaluations

To minimize burden, assessments, and interviews will be implemented while patients are at home or already on site for standard care. At the time of enrollment, participants will be provided a tablet computer to borrow for the study (unless they already have a comparable device that they prefer) and receive training on completing questionnaires either online or by telephone, similar to a training successfully implemented in a study of symptom monitoring in this patient population.[93] This prior study suggested that alternate data collection methods such as automated telephone calls may increase adherence to web-based symptom reporting.[93] Patient-reported questionnaires will be conducted at four time points: before surgery (baseline), one day after surgery, two weeks after surgery and 4 weeks after surgery.

We are most interested in assessing and then effectively managing acute within one week following surgery when pain is likely to be highest,[94] and how pain management during this period may ultimately impact longer-term pain. Daily diaries are one method for measuring an experience in a participant's natural setting with low patient burden.[95] Thus, participants will also be asked to complete daily surveys of outcomes and adherence to home practice of the intervention via REDCap and wear a wrist actigraphy device for up to one week before and one week following surgery. REDCap is a flexible electronic data capture system offered by the Wake Forest CTSI that will verify the date and time of assessments implemented via the internet, telephone, or paper. Our team has piloted the use of REDCap for implementing daily assessments during our ongoing study. Women with gynecologic malignancies have demonstrated reasonable compliance (86%) with electronic diary assessment[96] and daily assessments after gynecologic oncology surgery (68% compliance).[94] Participants will be prompted to complete the surveys (3-5 minutes) at approximately 6:00pm each evening and can complete the survey any time before they go to sleep. A paper guide with response options for the questionnaire will be provided to improve comprehension over the telephone. Participants will also be given a wrist actigraphy device and instructions for its use during this same time period.

In addition, demographic data will be patient-reported at baseline, medical records will be reviewed to obtain clinical data, treatment fidelity observed at the videoconference intervention session, and an interview conducted at a follow-up clinic visit or by telephone. Participants will be compensated up to $100 total for completing study assessments. We will also track recruitment, adherence to the videoconference intervention, any other contact with interventionists, completion of assessments, and any adverse events that may occur. Those who decline participation or drop out of the study will be asked for feedback about their choices.

6.2.1 Screening Evaluation

Consenting Procedure

If the patient is interested and referred by the physician, the Project Manager or other study team member will approach or call interested patients prior to surgery to

explain the protocol, answer questions, 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 electronically (via REDCap) or in person. Either a hard copy or email attachment of the informed consent document will be given to the participant, and the original copy will be kept in the participant's file. Each participant will be asked to separately agree to be videotaped for the study, which will not affect their ability to participate. If they do consent to be videotaped, they are told in the consent form that they can ask not to be included in the filming or withdraw their consent to be videotaped at any time. These videos are focused on the interventionist for the sole purpose of increasing treatment fidelity. We will also let participants know at the time of consent that it is their choice whether or not visitors remain in the room during the intervention and ask if they have a preference.

Screening

Screening evaluations will begin once a patient is scheduled for a consultation related to receiving surgery for a suspected gynecologic malignancy. 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 study team member to identify potential patients that meet enrollment criteria. This screening will consist of:

- Review of medical history
- Review of treatment plan

We will approach patients either in person or remotely (e.g., telephone, myWakeHealth, mail) 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.

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.

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. The baseline assessment may be completed within two weeks prior to surgery.

- *Assessment Completion/Retention.* Percent completion of planned standard and daily assessments.
- *Pain.* The Patient Reported Outcomes Measurement Information System (PROMIS) measure of pain of intensity (i.e., How would you rate your pain on average?), which has been adapted for assessing pain on a numeric rating scale from 0 (no pain) to 10 (worst imaginable pain) "in the last day,"[97] is the proposed primary outcome (at 2 weeks) for the future larger clinical trial that will be informed by the current study. Patient-reported pain is considered the 'gold standard' for pain assessment since pain is a subjective experience and PROMIS is supported by the NCCIH and National Cancer Institute.[98,99] Pain interference, the affective dimension of pain, and analgesic use will be assessed using 9 patient-reported items. *Pain interference* will also be assessed with a PROMIS measure (6-items).[97] The *affective dimension of pain* will be assessed with one item on a scale from 0 (not bad at all) to 10 (the most unpleasant feeling possible for me).[84,98,100] *Analgesic use* in the past 24-hours will be tracked daily for one week before and one week post-surgery (postoperative day 1 to 8; day added since participants may report information from the prior day) and converted to a cumulative analgesic consumption score for analysis (2-items).[101] We will also ask participants if they are taking any analgesic medication postoperatively.
- *Sleep Disturbance* will be assessed with a PROMIS Sleep Disturbance short-form (8-items)[102] adapted for daily use.
- *Psychological Distress.* The PROMIS Depression (8-item) & Anxiety (7-item) adapted short-forms will be used to assess psychological distress "in the last day."[97]

- *Pain Self-Efficacy* will be assessed with the pain management subscale of the Chronic Pain Self-Efficacy Scale,[103] which has been used postoperatively (5-items).[104]
- Daily Symptoms will be assessed for up to one week before surgery and week after surgery starting on postoperative day 1 (or as soon as feasible) using 4 items on pain (2), disturbed sleep, and distress. The same adapted PROMIS pain intensity item will be asked and sleep disturbance and psychological distress items will be used from the MD Anderson Symptom Inventory (MDASI), which asks about each symptom at "its worst" in the past 24 hours from the MDASI designed to be implemented daily[105] and used perioperatively.[94]
- *Sleep Disturbance* will also be assessed with *actigraphy*, a non-intrusive alternative to the traditional polysomnography when monitoring sleep.[106] The Actiwatch Spectrum model actigraph will be worn for up to 1 week before surgery and one week after surgery starting on postoperative day 1. This watch-like device measures rest/activity patterns in a natural setting, and provides summary measures of daily sleep activity. Sleep disturbance will be defined as a daily ratio of circadian disruption (the ratio of nighttime activity to daytime activity; higher scores show greater circadian disruptions). A similar device and the same ratio has been used in patients perioperatively.[107] Participants will also self-report the time spent napping and their bed and rising times daily.[108]
- *Demographic Factors.* Age, race/ethnicity, marital status, education level, ability to pay for the basics, distance travelled for care, medical history, previous use of mind-body practices, baseline level of mindfulness, and internet access will be self-reported at baseline.
- *Clinical Factors.* Cancer site, type of surgery stratified by risk,[109] treating physician, date diagnosed, other cancer treatments, comorbidities, height, weight, prescription medications for pain, sleep, depressive symptoms, and anxiety will be abstracted from medical charts at baseline.

Randomization

Randomization will occur the same day that screening is confirmed. Instructions for completing the intervention will begin at the same visit.

6.2.3 Blinding

- Participants will be told that both groups offer programs to support their experience in coping with surgery to match efficacy expectations.
- The study team member collecting outcome assessments will be blinded to group assignment.
- A complete description of each study arm will be presented to participants upon their completion of all study measures.

6.2.4 Follow-up Visits

The timing of study assessments is summarized in Table 1. Postoperative day 1 assessments may be completed within 3 days after surgery. The two-week and 4-week assessments can be timed with in-person follow-up visits, which may be

scheduled within a week of the scheduled assessment. Descriptions of additional measures not assessed at baseline include:

- *Adherence.* Completion of the videoconference session
- *Interventionist Communication.* Any additional contact with the interventionists.
- *Intervention Home Practice*. Use of the self-directed intervention (time and duration) will be measured daily for up to one week before and one week after surgery as assessed in another yoga study.[38] Self-reported time of practice will also be assessed retrospectively (in the past week) at postoperative weeks 2 and 4.
- *Acute Adverse Events.* Participants will also be asked to complete two Visual Analogue Scale items assessing pain intensity and psychological distress daily with the instructions to report their experience "right now," immediately before and after the intervention to detect any acute adverse events.[65]
- *Expected Benefit.* The HEAL Treatment Expectancy measure 6-items)[110] will assess expected benefit of the intervention following the videoconference session.
- *Daily Symptoms* will be assessed for up to one before surgery and week after surgery starting on postoperative day 1 (or as soon as feasible) for 8 days (since participants may report information from the prior day) using 3 items on pain, disturbed sleep, and distress. The same PROMIS pain intensity item will be asked and sleep disturbance and psychological distress items will be used from the MDASI, which asks about each symptom at "its worst" in the past 24 hours from the MDASI designed to be implemented daily[105] and used perioperatively.[94]
- *Sleep Disturbance* will also be assessed with *actigraphy*, a non-intrusive alternative to the traditional polysomnography when monitoring sleep.[106] The Actiwatch Spectrum model actigraph will be worn for up to 1 week before surgery and one week after surgery starting on postoperative day 1. This watch-like device measures rest/activity patterns in a natural setting, and provides summary measures of daily sleep activity. Sleep disturbance will be defined as a daily ratio of circadian disruption (the ratio of nighttime activity to daytime activity; higher scores show greater circadian disruptions). A similar device and the same ratio has been used in patients perioperatively.[107] Participants will also self-report their bed and rising times daily.[108]
- *Patient Provider Connection* will be measured with a 7-item short-form from the Healing Encounters and Attitudes Lists (HEAL)[110] at the 4-week follow-up visit.
- *Clinical Factors.* Medications prescribed for pain, length of stay, any complications experienced, and other cancer treatments, will also be abstracted four weeks post-surgery.

6.2.5 Completion/Final Evaluation

Assessments to be performed at the participant's final visit are described in the prior section. Participants who discontinue study the intervention early 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:

EMindful Movement and Breathing

- Emotional discomfort
- Muscle soreness

Active Control

- Emotional discomfort

Each interventionist will monitor and note any adverse events experienced during the videoconferencing (e.g., patients' experience of disturbed breath, expression of physical/emotional discomfort, or request to discontinue the in-person intervention sessions). In addition, study staff will ask participants if they experienced any problems when doing the home practices and review notes from the home practice logs at follow-up visits. Instructors will have phone numbers for the triage nurse and Cancer Support Services available to give to patients as referrals if patients tell them about any clinical issues that arise. Study staff will also document in the electronic patient records using a telephone note if a referral number was provided.

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 in bed movement, breathing and meditative practices or caring attention among people undergoing surgery for a suspected gynecologic malignancy. Similar yoga interventions have been conducted in patients with cancer with no published reports of adverse events, some which included participants during the perioperative period.[40,65] The PI conducted an initial pilot study of 10 participants with the proposed yoga intervention implemented perioperatively in-person at WFBCCC from 05/2012 – 05/2013.[65] There were no adverse events observed related to the yoga practice in this study.

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 Co-Investigators when

appropriate. The PI will initially assess if the AE is related to the study interventions as definitely, probably, possibly or unrelated.

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. Research staff will report AEs according to data safety monitoring plan. Events will be documented including date of event which will avoid double capture.

7.4 Reporting Procedures

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 Followup 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. 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.

1. **Primary Hypothesis:** We hypothesize that we will enroll at least 50% of eligible patients, participants will adhere to 70% of the interventions, and at least 70% of participants will complete study assessments and be retained in the study.

Secondary:

2. We will describe any adverse events reported as frequencies.

3. Assess descriptive data on proposed outcomes (i.e., pain [primary outcome - pain interference at week 2], sleep disturbances, psychological distress) for the next phase of study;

   The Patient Reported Outcomes Measurement Information System (PROMIS) measure of pain of intensity (i.e., How would you rate your pain on average?), which has been validated for assessing pain on a numeric rating scale from 0 (no pain) to 10 (worst imaginable pain) "in the last day,"[97] is the proposed primary outcome (at 2 weeks) for the future larger clinical trial that will be informed by the current study. Patient-reported pain is considered the 'gold standard' for pain assessment since pain is a subjective experience and PROMIS is supported by the NCCIH and National Cancer Institute.[98,99]

4. Qualitatively assess acceptability to guide future study planning.

9.2 Sample Size and Randomization

The target sample size is based on the goals of estimating the rates of feasibility measures (i.e., recruitment, adherence, assessment completion, adverse events and retention rates) to inform the design of a larger efficacy trial. This current pilot study is not designed to assess the effect of the eMMB on any outcome. Thus, we will accrue a total of 31 participants, because this number provides reasonably tight estimates of our parameters of interest. We will be able to estimate these rates within +/- 18% using a two-sided 95% confidence interval, and within 9-15% using a one-sided interval (dependent on the observed proportion). If the recruitment rate is below 50% and the adherence and retention rates are below 70% (i.e., 30% drop-out or non-adherence), a larger study may not be feasible. That is, with an observed retention rate of ≥80% (20% lost to follow-up, target N=25 and lost to follow-up N=6) we can be highly confident that the true rate is at least 68% (the lower limit of a one-sided 95% CI for an observed rate of 80% is 68.2%). An adequate retention rate for Week 2 data will be an indicator that this study is successful and we are ready to proceed to the next phase of study.

Power calculations for a subsequent larger study will be based on clinically meaningful differences between the groups on the primary outcome.[112] The number of participants interviewed (20-31) will be determined when data saturation is

reached. As is conventional for thematic analysis, we will conduct interviews until we think there is enough qualitative data to address issues related to the acceptability of study procedures. [113] The study team's experience leads us to believe that 10-15 interviews from each of the two arms will be sufficient to achieve this objective. Our analyses of differences between cancer type and invasiveness will be for exploratory purposes and therefore data saturation using those variables is not the goal. If unexpected information emerges and our timeline allows, we will consider amending the protocol to recruit additional participants.

Treatment Assignment Procedures

Eligible, consented, and enrolled participants will be randomized to eMMB or AC. To control for type of cancer and invasiveness of surgery, randomization will occur within cancer type (uterine or ovarian) and surgery type (laparotomy or robotic). There is not a sample size goal within strata.

Randomization (1:1) lists within each strata will be generated. Study team members who are collecting outcome data will not be informed of group assignment.

9.3 Definition of Populations

We will use the revised CONSORT 2010 guidelines for intention-to-treat (ITT) analysis of randomized control trials[114] 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.[115] 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 pilot findings will be generalizable to will be that represented by the sample meeting our requirements for inclusion in the ITT sample.

9.4 Interim Analyses and Stopping Rules

There are no interim analyses planned for this clinical trial. Summaries of process variables (i.e., recruitment, adherence, data collection, adverse events, retention) will be conducted on a rolling basis as the study progresses. The PI will present data on subject accrual to the Independent Monitoring Committee (IMC). Based on the Cancer Registry at WFBCCC from 2015-2017 an average of 128 patients/year had surgery for uterine or ovarian cancer (73% uterine; 27% ovarian). Therefore, assuming 80% of patients are eligible (n=102), and that we can recruit about 30-50% of those eligible (n= 31-51), we anticipate recruiting 31 participants over approximately 8-16 months (2-4 per month). Fidelity of implementing the interventions will also be 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 study team member collecting outcome data will be masked to the participant's intervention group assignment.

9.5.1 Primary Outcome

The primary study outcome is feasibility (i.e., recruitment, adherence, assessment completion, and retention rates)

9.5.2 Secondary Outcomes

Secondary outcomes include proposed outcomes (i.e., pain [primary outcome - pain interference at week 2], sleep disturbances, psychological distress) for the next phase of study. The Patient Reported Outcomes Measurement Information System (PROMIS) measure of pain of intensity (i.e., How would you rate your pain on average?) is the proposed primary outcome (at 2 weeks) for the future larger clinical trial that will be informed by the current study.

Adverse events and qualitative data will also be collected.

9.6 Data Analyses

This study will provide quantitative data on recruitment, adherence, assessment completion, adverse events and retention rates and qualitative assessment of acceptability to guide future study planning. We will calculate 95% confidence intervals for each of the feasibility measures to determine the range of estimates that are consistent with our data. We will track the number of screened participants, those who are eligible, and the percent who agree to participate. For those not meeting the eligibility criteria, reasons will be summarized. The proportion of participants and corresponding 95% CI for participants who participated in the eMMB and AC sessions and those who completed all assessments will be computed; we will also calculate the frequency of any adverse events and percent of participants who complete the 2w visit to assess retention. We will use one-sample tests of binomial proportions to compare the recruitment, adherence, and retention rates to the hypothesized values of 50%, 70% and 70%, respectively. In exploratory analyses, we will compare participants who are non-adherent or who drop out by demographic characteristics, intervention group, and baseline scores of the measures. We will also investigate any differences in participant recruitment, adherence, assessment

completion, adverse events, and retention rates by surgery type and cancer type to identify an optimal patient population for a future study.

Baseline analyses will include descriptive statistics of pain (i.e., intensity, interference, affective, analgesic use), sleep disturbance (patient-reported), psychological distress, background characteristics (i.e., demographic) and other possible confounding variables (e.g., type of cancer, type of surgery, medications) by intervention group. The distributions of continuous variables will be examined to determine the presence of outliers and whether transformations are necessary for analysis. The primary goal of the statistical analysis of these measures for this Aim will be to estimate standard deviations (SD) for use in future studies. Additional analyses will include fitting mixed ANCOVA models (adjustment for baseline) to model the trajectory of pain (and sleep disturbance and distress) by time and group accounting for the repeated measures on a subject; if any meaningful differences between the groups are found at baseline, we will include them in these models. Analgesic use will be modeled in a similar manner using a GEE model with a logit link. We will also use mixed models to examine the daily actigraphy, pain, and other symptom data by group and time. The purpose of all of these models will be to obtain estimates of the SD of change adjusted for covariates of interest and the within-person correlation of the repeated measures, not to perform formal hypothesis testing. In exploratory models we will examine the impact of adherence to eMMB on changes in the measures, subgroup analysis by surgery type, and we will examine the role of pain self-efficacy as a potential mechanism. The purpose of these analyses will be to estimate SD and within-person correlation by subgroup and with adjustment for mechanisms; no formal hypothesis testing will be done. We will also examine the validity of the patient report for intervention practice by examining the concordance between the self-report of MMB practice and the activity level on the accelerometer.

Interview transcripts will be coded independently by two staff members of the QPRO Core. Twenty-five percent of the transcripts will be coded independently by two separate coders to ensure consistency of code application. Unresolved discrepancies reconciled by a third person. Using thematic analysis, the coded text will be iteratively reviewed and interpreted.[113] The qualitative and quantitative analyses will be evaluated in a mixed-methods framework for consistency and discrepancies to refine the protocol for future studies. For example, if the qualitative interviews indicate that a particular subgroup of patients (e.g., by cancer type, surgery type) perceive greater benefit from the eMMB, then we will perform exploratory subgroup analysis of the quantitative data.

10. DATA COLLECTION AND QUALITY ASSURANCE

10.1 Data Collection Forms

Questionnaires will be collected by a blinded study team member (Clinical Studies Coordinator). Questionnaires will either be completed directly in REDCap or using paper forms. 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 WFBCCC or in the PI's office building while on study. 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.

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 study team member 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.

Outcomes and stored as summarized in the following table.

Summary of Data Storage

Informed consent document	Electronic Medical Record
Protocol registration form	OnCore
Study questionnaires	REDCap
Daily survey data	REDCap
Treatment fidelity data	REDCap
Clinical data	REDCap
Actigraphy data	Excel Files on Secure Server
Adherence data	REDCap
Qualitative data	Files on Secure Server
Adverse events	OnCore

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 to ensure that a sufficient number of participants are being enrolled and that they meet the targeted ethnic diversity goals outlined in the grant proposal.

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 collected via paper questionnaires. 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 another study team member 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, 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