**University of Iowa**
**Holden Comprehensive Cancer Center**

**Observational or Low-Risk Interventional Protocol**

# Title: Living Well: A Web-Based Program to Improve Quality of Life in Rural and Urban Ovarian Cancer Survivors


**Principal Investigator:**

Susan K Lutgendorf, Ph.D.
G60 Psychological and Brain Sciences Building
Telephone: 319-335-2432
Fax: 319-335-0191
susan-lugendorf@uiowa.edu

**Sub-Investigators:**

Michael Goodheart, MD
Department of Obstetrics and Gynecology
Division of Gynecologic Oncology
31506 PFP
(319)-356-2015

Barbara Norquist, MD
Department of Obstetrics and Gynecology
Division of Gynecologic Oncology
University of Washington Cancer Consortium

Frank Penedo, Ph.D.
Department of Psychology and Sylvester Cancer Center, University of Miami

Matthew Schlumbrecht, MD, MPH, FACOG
Division of Gynecologic Oncology
University of Miami

**Biostatistician:**

Bridget Zimmerman, Ph.D.
Department of Biostatistics

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| **Primary Research Coordinator**: | Sharaf Zia, M.A. |
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| **Version:** | 3.15 |

**SUMMARY OF CHANGES**

| Section | Change |
|---|---|
| **30 September 2020** | **Version 2.0 to 3.0** |
| Cover Page | Updated University of Washington and UW abbreviation throughout to Fred Hutch/University of Washington Cancer Consortium |
| Page 3,6 | Updated amendment version and date. |
| Page 4 | 2 training sessions now included |
| Page 7 | HL renamed Healthy Lifestyles; HP changed to HL throughout |
| Page 11 | PHQ-9 replaced with CES-D for depression screening. Substance abuse criteria limited to last two years, active suicidality removed from exclusion |
| Page 13 | Patient contact process updated |
| Page 14 | Patient contact process updated, PHQ-9 replaced with CES-D |
| Page 15 | Randomization, trainings, and process language updated |
| Page 16 | Randomization, trainings, process language, and table updated. Webcams added in addition to tablets. |
| Page 18 | PHQ-9 replaced with CES-D for depression screening |
| 14 January 2021 | Version 3.0 to 3.1 |
| Page 10 | Inclusion criteria updated |
| Page 15 | Randomization, trainings, and process language updated |

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|---|---|
| Page 15 | Participant scheduling process updated |

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|---|---|
| 25 February 2021 | Version 3.1 to 3.2 |
| Page 16 | Study activities updated |

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|---|---|
| 2 April 2021 | Version 3.2 to 3.3 |
| Page 14 | Recruitment and screening process updated |
| Page 15 | Study activities updated |
| Page 18 | PHQ-9 replaced with CES-D for depression screening |

| | |
|---|---|
| 26 May 2021 | Version 3.3 to 3.4 |
| Page 10 | Inclusion criteria updated |
| Page 11 | Exclusion criteria updated |
| Page 16 | Study activities updated |

| | |
|---|---|
| 18 June 2021 | Version 3.4 to 3.5 |
| Page 11 | Inclusion criteria updated |
| Page 11 | Exclusion criteria updated |
| Page 16 | Study activities updated |

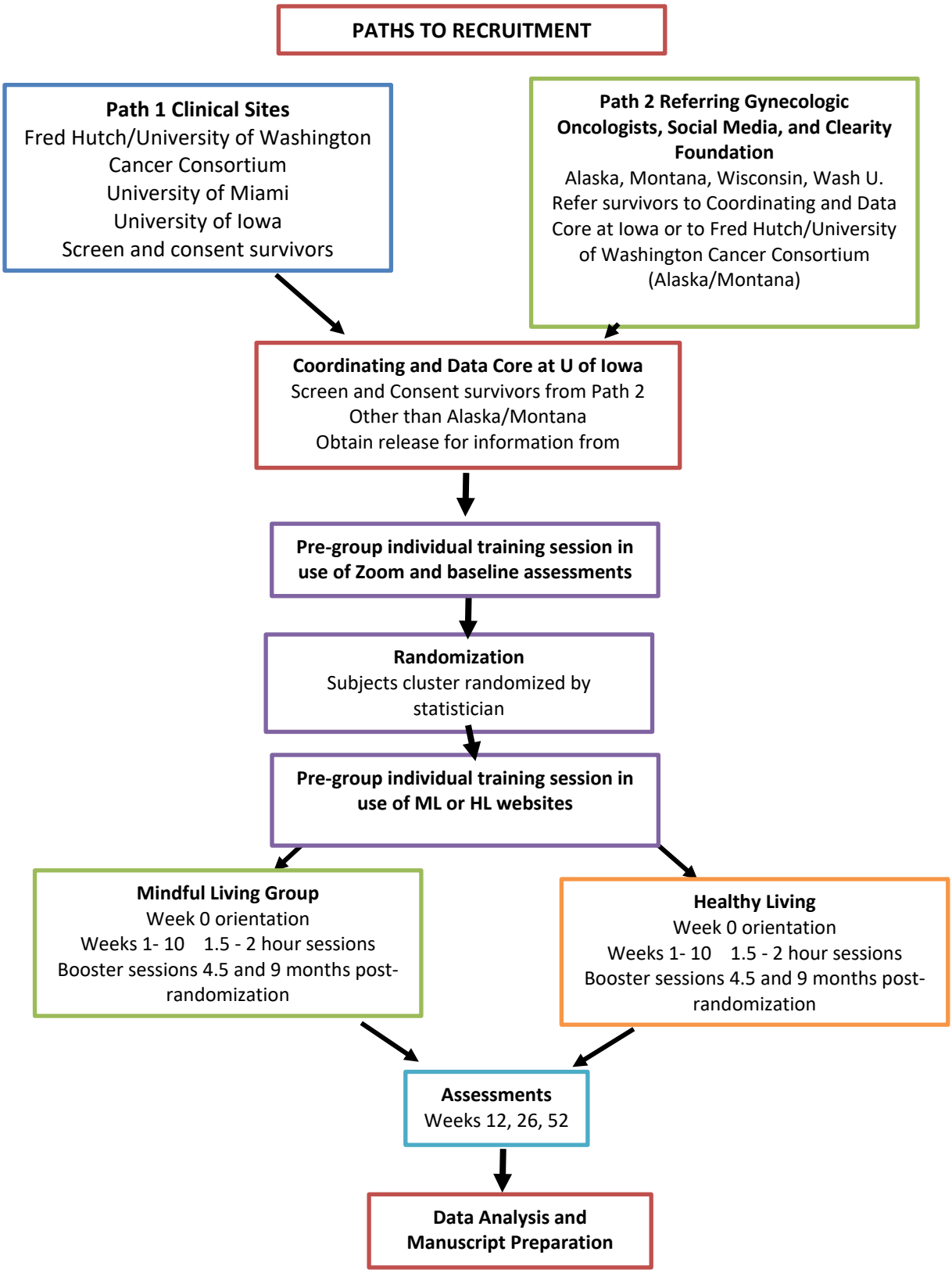
| | |
|---|---|
| 23 August 2021 | Version 3.5 to 3.6 |
| Page 10 | Inclusion criteria updated |
| Page 11 | Exclusion criteria updated |
| Page 13 | Study activities updated |

| | |
|---|---|
| 3rd September 2021 | Version 3.6 to 3.7 |
| Page 12 | Temporary and Full Exclusion criteria updated |
| 7th December 2021 | Version 3.7 to 3.8 |
| Page 17 | Study Activities |
| 22nd February 2022 | Version 3.8 to 3.9 |
| Page 17 | Study Activities |
| 28 March 2022 | Version 3.9 to 3.10 |
| Page 10,11 | Study Goals Updated |
| Page 11 | Study Population Updated |
| Page 12 | Inclusion Criteria Updated |
| Page 15,16 | Study Procedures Updated |
| Page 19 | Study Activities Updated |
| Page 22 | Risks Updated |
| 13th April 2022 | Version 3.10 to 3.11 |
| Page 18,19 | Study Activities |
| 4th May 2022 | Version 3.11 to 3.12 |
| Page 19 | Study Activities |
| 10th Oct 2022 | Version 3.12 to 3.13 |
| Page 17,18 | Study Activities |

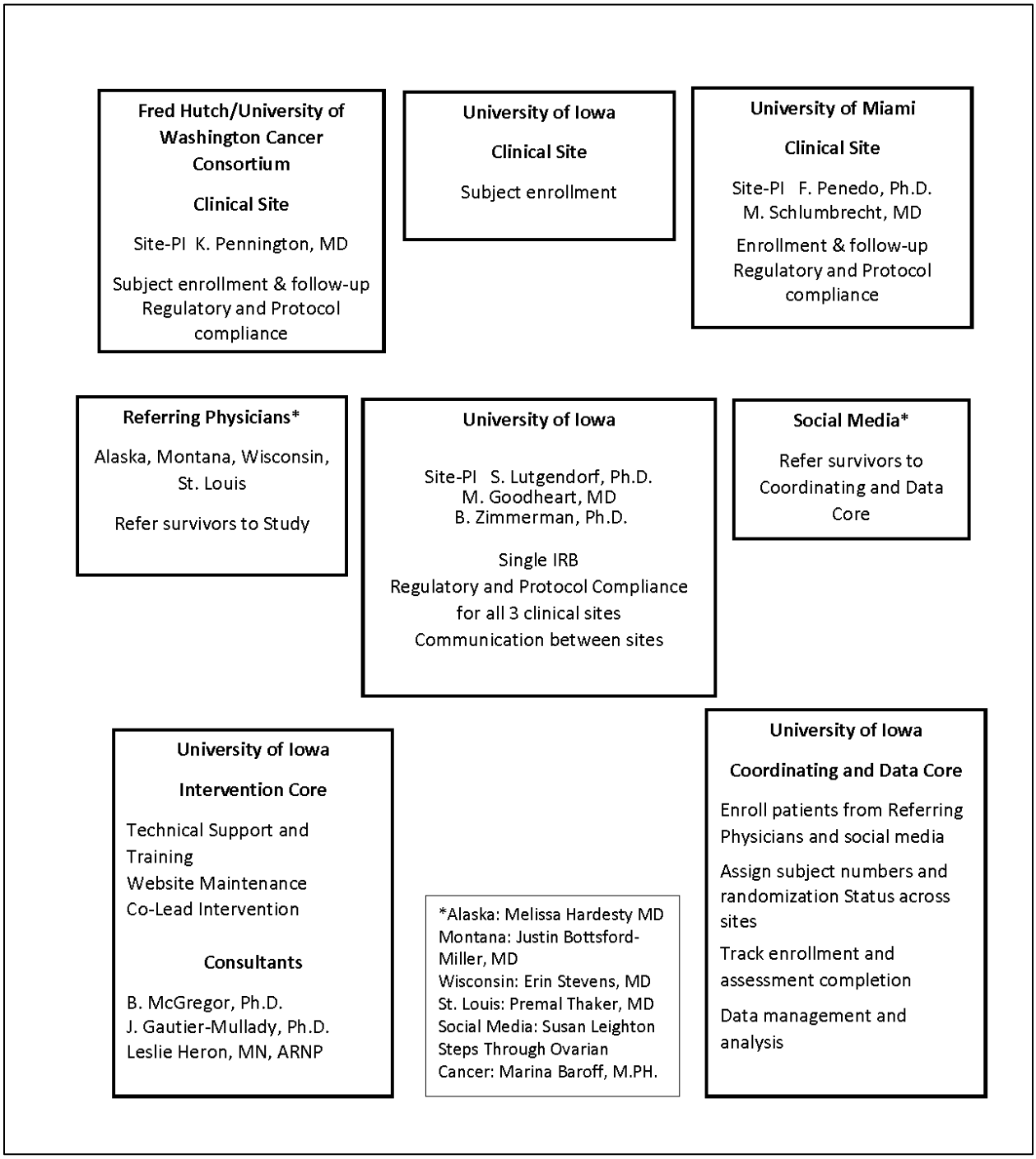
| | |
|---|---|
| 10th Oct 2022 | Version 3.13 to 3.14 |
| Page 20 | Study Activities |

| | |
|---|---|
| 7th August 2023 | Version 3.14 to 3.15 |
| Page 19 | Study Activities |
| | |
| 9 October 2024 | Version 3.15- 3.16 |
| Pages 24-25 | Statistical Evaluation updated |
| Page 1 | UW collaborator updated |

## TABLE 1. SCHEMA



## Table 2. ORGANIZATIONAL TABLE



**REVISION HISTORY**

**Version 3.1 Version Date 2.25.21**

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| LIST OF ABBREVIATIONS | |
|---|---|
| CBSM | Cognitive Behavioral Stress Management |
| HRQOL | Health related quality of life |
| MBSR | Mindfulness-Based Stress Reduction |
| ACT | Acceptance and Commitment Therapy |
| HL | Healthy Lifestyles |
| RCT | Randomized Controlled Trial |
| STOC | Steps Through Ovarian Cancer |
| UI | University of Iowa Holden Comprehensive Cancer Center |
| UW | Fred Hutch/University of Washington Cancer Consortium |
| UM | University of Miami Sylvester Comprehensive Cancer Center |
| RA | Research Assistant |
| PHI | Protected Health Information |
| FACT-O | Functional Assessment of Cancer Therapy-Ovarian |
| CES-D | Center for Epidemiological Studies-Depression Scale |
| POMS-SF | Profile of Mood States Short Form |
| TMD | Total mood disturbance |
| FACIT-F | FACIT Fatigue Inventory |
| OC | Ovarian Cancer |
| SPS | Social Provisions Scale |
| MOCS | Measurement of Current Status |
| FMI | Freiburg Mindfulness Inventory |
| AAQ-2 | Acceptance and Action Questionnaire |
| BEAQ | Brief Experiential Avoidance Questionnaire |
| PSQI | Pittsburgh Sleep Quality Index |
| RUCC | US Department of Agriculture's Rural Urban Continuum Codes |
| PHQ-9 | Patient Health Questionnaire-9 |
| WRAT | Wide Range Achievement Test |
| ML | Mindful Living |
| CBT | Cognitive Behavioral Therapy |
| PHQ | Personal Habits Questionnaire |

## 1. Abstract

Over the last two decades, it is well documented that the chronic and often debilitating experience of ovarian cancer survivorship may include poor health-related quality of life (HRQOL), elevated anxiety and depression, poor sleep, fatigue, multiple symptoms/side effects, existential concerns, and a generally poor prognosis. Because of compromises to many aspects of HRQOL combined with low rates of survival for the majority of these patients, development of innovative approaches for improving HRQOL and potentially improving clinical outcomes is of paramount importance. This need is particularly true in rural settings where women may have less access to clinic-based support systems. Despite the multiple challenges experienced by ovarian cancer survivors, research targeting the potential efficacy of psychosocial interventions in enhancing HRQOL has been extremely limited. Over the last several years a 11-week group-based and web-delivered psychosocial intervention now entitled Mindful Living, targeting key concerns of ovarian cancer survivors has been developed and piloted with input from survivors. The overarching goal of the current project is to examine the efficacy of the Mindful Living intervention verses a Health Promotion active control intervention called “Healthy Living” in a cluster-randomized Phase II clinical trial. It is hypothesized that the Mindful Living intervention will be efficacious in improving HRQOL and decreasing perceived stress and depressive mood. This application is highly innovative because it combines elements of evidence-based psychosocial interventions in a novel way to target the needs of ovarian cancer survivors using a state-of-the-art web-based platform that has the potential for wide dissemination. This work is highly translational as it is a direct application of findings from mechanistic stress-related research to testing an intervention to reduce stress in ovarian cancer survivors. The significance of the application is that this intervention has the potential to overcome prior barriers to the implementation of such psychosocial interventions and improve HRQOL, thus providing public health benefits to an understudied and compromised cancer population with a high likelihood of recurrence.

## 2. Background / Rationale

Although ovarian cancer ranks second in incidence among gynecologic cancers, more women die from ovarian cancer than from all other gynecologic cancers combined. Over the last two decades, it is well documented that the chronic and often debilitating experience of ovarian cancer survivorship which may include poor quality of life (HRQOL), elevated anxiety and depression, poor sleep, fatigue, multiple physical symptoms/side effects, existential concerns, and a generally poor prognosis.[1–9] Additionally, factors such as social isolation, stress, and/or depression are associated with key biological processes promoting tumor progression as well as poorer survival.[10–15] These data have been supported by parallel findings in animal and in in vitro models.[11,16–22] Because of compromises to many aspects of HRQOL, combined with low survival rates for most patients, development of innovative approaches for improving HRQOL and potentially impacting disease progression is of paramount importance. This need is particularly true in rural settings where women may have less access to clinic-based support systems.

Despite the multiple challenges experienced by ovarian cancer survivors, research targeting the potential efficacy of psychosocial interventions in enhancing HRQOL has been extremely limited. Barriers to development and implementation of group-based interventions for ovarian cancer survivors have included: a) a limited population of ovarian cancer survivors at any one site; b) extensive distances between home and gynecologic oncology specialized care; and c) debility that would prohibit travel to participate. The proposed intervention is ideally suited to overcome these barriers. Over the last several years a 11-week group-based and web-delivered psychosocial intervention entitled *“*Mindful Living” targeting key concerns of ovarian cancer survivors has been developed and piloted with input from survivors. The program draws from core elements of Cognitive Behavioral Stress Management (CBSM), Mindfulness-Based Stress

Reduction (MBSR), and Acceptance and Commitment Therapy (ACT). The intervention has been shown to be feasible and acceptable, and preliminary data indicate increases in HRQOL and decreases in perceived stress and depression among ovarian cancer survivors in one-armed field trials.[23] A Health Promotion comparator intervention (Healthy Living) has also been tested. The overarching goal of the current project is to examine the efficacy of the Mindful Living intervention verses a Health Promotion active control intervention in a cluster-randomized Phase II clinical trial. This application is highly innovative because it combines elements of evidence-based psychosocial interventions in a novel way to target the needs of ovarian cancer survivors, using a state-of-the-art web and video conferencing platform that allows wide dissemination, including to rural survivors. This work is highly translational as it is a direct application of mechanistic stress-related research findings to a scalable intervention designed to reduce distress and improve HRQOL in a broad audience of ovarian cancer survivors. The significance of the application is that this intervention has the potential to overcome prior barriers to the implementation of such psychosocial interventions and improve HRQOL thus providing public health benefits to an understudied and compromised cancer population with a high likelihood of recurrence.

## 3. Study Goals/Objectives

The main objective of the current study is to determine the efficacy of a group-based and web-delivered psychosocial intervention for ovarian cancer survivors (Mindful Living [ML]) compared to a Health Promotion attention-matched condition (Healthy Lifestyles [HL]) in increasing HRQOL and decreasing perceived stress, depressive mood, anxiety, and fatigue across a 12-month period.

Subjects will also be able to participate in an optional Immune Marker Sub-Study. This sub-study is being done to gather preliminary data on effects of the Mindful Living intervention on inflammatory biology in a subset of study participants using home collection of dried blood spots (DBS). The sub-study will examine expression of the conserved transcriptional response to adversity (CTRA), a 53-gene composite associated with chronic stress, as well as involvement of lymphocyte subsets.

**Specific Aim 1.** To determine the efficacy of a group-based and web-delivered psychosocial intervention for ovarian cancer survivors compared to a Health Promotion attention-matched condition in increasing HRQOL and decreasing perceived stress, depressive mood, anxiety, and fatigue across a 12-month period.

- ***Hypothesis 1:*** Subjects in the Mindful Living intervention will show greater increases in **HRQOL** and greater decreases in **perceived stress** and **depressive mood (primary outcomes)**, anxiety, and fatigue **(secondary outcomes)** compared to HL subjects.
- ***Rationale***: This aim tests the effects seen in one-armed preliminary trials in a randomized controlled trial (RCT) with a well-powered cohort and long-term follow-up.

**Specific Aim 2.** To determine whether the skills provided in Mindful Living (i.e., **cognitive reframing, relaxation, mindfulness- and acceptance-based skills**) mediate the effects of Mindful Living on these outcome measures.

- ***Hypothesis 2a:*** Subjects in the *Mindful Living* intervention will show a greater acquisition of relaxation, mindfulness, acceptance, and cognitive coping skills compared to those in the HL group.
- ***Hypothesis 2b:*** Subjects with greater increases in mastery in relaxation, cognitive coping, mindfulness, and acceptance skills will show greater increases in HRQOL and greater decreases in perceived stress, depressive mood, anxiety, and fatigue.

- ***Rationale***: Our preliminary data and research by other groups(Antoni, Kazi et al. 2006) has shown that greater acquisition of intervention-based skills mediates the effects of the interventions.

**Exploratory Aim 3.** To determine whether the effect of the intervention varies across several factors such as rural vs. urban residence, recurrence status, age, disease stage, or time since diagnosis.

**Exploratory Aim 4.** To characterize effects of the Living WELL intervention in ovarian cancer survivors on inflammatory biology in peripheral blood cells as assessed with dried blood spot technology.

- ***Hypothesis 4a:*** Peripheral leukocytes from ovarian cancer survivors in the Mindful Living intervention will show less polarization towards a pro-inflammatory CTRA profile from pre-intervention to post-intervention compared to those in the Health Promotion condition.
- ***Hypothesis 4b:*** Peripheral leukocytes from ovarian cancer survivors in the Mindful Living intervention will show less CD14 (monocyte) mRNA prevalence from pre-to post intervention compared to those in the Health Promotion condition.
- ***Hypothesis 4c:*** Greater decreases in depression and perceived stress and increases in HRQOL from pre-to post intervention in both groups will be associated with decreased polarization towards a pro-inflammatory CTRA profile.
- ***Rationale***: Prior evidence has shown significant interaction between inflammatory profiles and healthcare outcomes in survivors of ovarian cancer.

## 4. Study Population

Subjects will be 256 women with epithelial ovarian, fallopian tube, peritoneal cancer, or cancer of Mullerian origin between the end of initial treatment and 5 years after completion of initial therapy with no more than one recurrence and not currently on chemotherapy for active disease. The study will include three clinical sites. Survivors will be recruited from Gynecologic Oncology Services at 3 clinical sites: the University of Iowa Holden Comprehensive Cancer Center (UI), the University of Miami Sylvester Comprehensive Cancer Center (UM), and the Fred Hutch/University of Washington Cancer Consortium (UW). In addition to these clinical sites, to increase our rural representation, we will also receive referrals from gynecologic oncology colleagues at Alaska Women's Cancer Care (Anchorage, AK), Billings Clinic in Montana, and HSHS St. Vincent Hospital in Green Bay, Wisconsin, all of whom serve at least 50% rural patients, and from Washington University (St. Louis) where approximately 33% of ovarian cancer patients are rural. We will also recruit from postings on social media by survivor advocate and survivor Susan Leighton and from Steps Through Ovarian Cancer: Support for Life with Ovarian Cancer (STOC), a new non-profit created by the Clearity and Susan Poorman Blackie Foundations. Based on our previous retention rates, and that of similar studies,[24–26] we anticipate up to a 25% attrition rate over the course of the intervention and follow-up. Thus to randomize 16 cohorts of 8 survivors to each condition, approximately 256 survivors will need to be recruited to yield a final sample of 192.

### Inclusion/Exclusion Criteria

Survivors aged 18 and older with a cytological or histological diagnosis of any stage of epithelial ovarian cancer, peritoneal cancer, fallopian tube cancer, or cancer of Mullerian origin consistent with ovarian/fallopian tube/peritoneal origin and who have not had more than one recurrence, will be eligible following completion of active chemotherapy and up to 5 years after completing primary

chemotherapy. We will not recruit survivors who are younger given the extremely low prevalence of ovarian cancers among females under 18.

## 4.1 Inclusion Criteria

1. Survivors 18 years or older with a cytological or histological diagnosis of any stage of epithelial ovarian cancer, peritoneal cancer, fallopian tube cancer, or cancer of Mullerian origin consistent with ovarian/fallopian tube/peritoneal origin (not consistent with endometrial cancer). Individuals diagnosed with synchronous ovarian and endometrial cancer primaries may be included if the initial endometrial cancer was stage I.[22]
2. Survivors who have completed primary treatment (surgery and chemotherapy or chemotherapy alone for a new diagnosis ovarian/peritoneal/fallopian tube cancer within the last 5 years). Date of completion of primary treatment is defined as within approximately 60 days after the last chemotherapy infusion. Maintenance therapy infusions do not count in determining date of completion of primary therapy. Women who were not recommended to receive adjuvant chemotherapy (for example, in the case of certain stage IA/IB cancers) are eligible after surgery alone. Women receiving consolidation or maintenance therapy following primary chemotherapy or following treatment for first recurrence are eligible.
3. Survivors must not have had more than one recurrence. Those who have had one recurrence will be eligible if they have completed active therapy for their recurrence.[27]
4. Although most women meeting the above criteria will be in remission, complete clinical remission (normal tumor markers and normal CT scan) is not a requirement for eligibility. Even women with low-level disease after completion of cytotoxic chemotherapy who do not meet the strict definition of remission may have stable disease and may not require additional cytotoxic chemotherapy for a prolonged period of time, particularly if they are on maintenance therapy. If subjects recur during the group they will be allowed to continue to participate, as able, even while taking chemotherapy.
5. Survivors must be fluent in spoken English ($6^{th}$ grade level), which is necessary to participate in the intervention.
6. Survivors must be willing to be randomized and followed for 12 months
7. Ability to understand and the willingness to sign a written informed consent document
8. Survivors receiving active treatment for another cancer may be eligible when their treatment is completed.

## 4.2 Temporary Exclusion Criteria

1. Survivors involved in Steps through OC must wait until they have completed that program to participate.
2. Survivors currently involved in a study involving another behavioral intervention or an exercise intervention must wait until the prior study is over to participate. (In cases 1 and 2, the temporary exclusion will end once survivors have completed their Steps through OC or behavioral intervention or exercise intervention. Study team will note down the date when Steps through OC or the behavioral intervention will end. At this point, the study team will recontact survivors and consent them to the study if they wish to participate.)
3. Survivors who score greater than or equal to 24 on the CESD can be rescreened when their depressive symptoms resolve. (In case 3, temporary exclusion will end when a survivor feels that their depressive symptoms have resolved, at which point they will retake the online screening on their own. If survivor's score on the CES-D of the online screening is less than 24 on rescreening, the study team will approach them to be consented if they wish to participate.)

## 4.3 Exclusion Criteria

1. Non-epithelial ovarian cancer, ovarian tumors of low malignant potential ("borderline"), cancers originating from other organs. Survivor who have a history of a prior cancer besides their ovarian cancer will be considered eligible as long as they are not in active therapy for said other prior cancer.
2. History of prior inpatient psychiatric treatment for severe mental illness (e.g. psychosis) or current psychosis, history of bipolar disorder or schizophrenia in the last 2 years or current bipolar disorder or schizophrenia, current major depression (CESD ≥ 24), dementia, history of substance use disorder in the last 2 years or current substance dependence, or organic mental disorder (e.g., dementia).
3. Survivors who are younger than 18 or older than 90 years of age
4. Unable to meet study requirements.
5. Currently receiving primary chemotherapy.
6. History of depression is not excluded as long as the survivor is not currently depressed (see #7).
7. Survivors who are currently depressed as indicated by a CES-D Score ≥ 24. (As indicated in 4.2.3 above, they can be rescreened once the depressive symptoms resolve.)

## 4.3 Inclusion of Minorities

Members of all races and ethnic groups are eligible for this trial.

## 5. Study Design and Methods

### 5.1. Primary Outcomes (Endpoints)

Health Related Quality of Life: The Functional Assessment of Cancer Therapy-Ovarian (FACT-O) includes 4 subscales related to dimensions of HRQOL, including physical, functional, social, and emotional well-being and a 12-item ovarian cancer-specific subscale related to ovarian cancer and treatment-specific HRQOL issues.[28,29]

Current Stress: The Perceived Stress Scale[30] contains 14-items assessing feeling in control vs. overwhelmed with current stressors over the last month. Internal reliability and construct validity are high[31] and scores have previously been associated with illness markers.[12,32,33]

Depressive Symptoms: The Center for Epidemiological Studies-Depression Scale (CES-D) is 20-item measure rating frequency of depressive symptoms over the past week. Scores of 24 or higher are associated with severe clinical depression.[34,35] The CES-D and its subscales have been strongly related to physiological variables in previous ovarian cancer research.[12]

### 5.2. Secondary Outcomes

Distress/Fatigue/Anxiety: The Profile of Mood States Short Form (POMS-SF)[36] is a validated scale listing 37 mood adjectives over the last month. Six factors have been identified: anxiety, dysphoria, anger, vigor, fatigue, and confusion. A total mood disturbance (distress) score (TMD) is calculated by summing the 5 negative mood factors minus vigor. The POMS has good reliability and validity, and has been widely used to assess distress in cancer populations.[37]

The FACIT Fatigue Scale is a short, 13-item survey tool that measures an individual's level of fatigue during their usual daily activities over the past week. The level of fatigue is measured on a four-point Likert scale (4 = not at all fatigued to 0 = very much fatigued)[38].

The Cancer Worry Scale assesses fear of cancer recurrence in patients and survivors of a variety of different cancers. The 6-item version of the Cancer Worry scale has been shown to have good construct validity, convergent and divergent validity, and high internal consistency.[39] As fear of recurrence is very salient in OC survivors, we are assessing this to achieve greater specificity in understanding anxiety.

Social Support: The Social Provisions Scale (SPS) is a 24-item self-report scale measuring perception of social support in current relationships. The scale has demonstrated adequate reliability and validity.[40] The total scale and attachment subscale have been highly correlated to physiological measures in previous work with OC patients.[13,14,41]

### 5.3. Potential Mediating Variables

Coping: The Brief COPE[42] is a 28-item survey assessing ways of coping with an individual's life stress. It includes both adaptive and maladaptive coping and has been widely used in cancer research.

Skills Acquisition: The Measurement of Current Status (MOCS) assesses skill acquisition from an intervention, including ability to relax, recognize stress-inducing situations, restructure maladaptive thoughts, and choose appropriate coping responses. Subjects indicate their degree of confidence for each skill on a 5-point scale. Effects on this scale have been shown to mediate effects of a stress management intervention.[43]

Mindfulness: Freiburg Mindfulness Inventory (FMI)[44] is a 14-item instrument measuring aspects of mindfulness including the acceptance of experience and a non-judgmental stance.

Experiential Avoidance: Acceptance and Action Questionnaire (AAQ-2) is a 10-item scale measuring a person's experiential avoidance along with acceptance and action[45,46] that is used quite widely in outcome studies of ACT interventions. Because of concerns that this instrument is too influenced by neuroticism,[47] we will also use the Brief Experiential Avoidance Questionnaire (BEAQ) a 15-item scale focusing on acceptance and avoidance.[48]

### 5.4. Demographic and Clinical Characteristics and Control Variables

Demographic and lifestyle characteristics including age, race, ethnicity, relationship status, rural/urban residence, education, income, sleep, mental health history, and physical activity will be assessed as possible confounds. The 4-item Godin Leisure Time Physical Activity survey[49] the Women's Health Initiative Personal Habits Questionnaire[50] will be used to assess physical activity, and the Pittsburgh Sleep Quality Index (PSQI) will be used to assess sleep quality.[51] We will monitor (self-report) for use of psychotherapy, psychotropic medications (e.g. antidepressants, anti-anxiety medications), and service utilization (e.g., support groups) at each assessment point and control for these if necessary. Rural residence will be categorized by the US Department of Agriculture's Rural Urban Continuum Codes (RUCC) which distinguish counties by degree of urbanization and adjacency to metropolitan areas.[52] Codes 4-9 have often been used to indicate rurality (non-metro),[53] whereas 7-9 have been used to indicate more isolated rural locations.

Data regarding stage, grade, pathology, recurrence, treatment, and medications will be abstracted from medical records. Subjects who come through non-clinic referrals will be asked to provide contact information for their physician and sign a release of information form as part of the consent process to verify self-reported clinical information. We will request the pathology report, most recent clinic notes, and patient insurance status.

## 6. Study Procedures

### 6.1. Recruitment

There are two paths to recruitment and screening. Path 1 is at the clinical sites (UI, Fred Hutch/University of Washington Cancer Consortium, UM), where potential study subjects will be identified by the collaborating gynecologic oncologist or a member of the health care team. Potentially eligible study subjects with upcoming appointments will be identified by the collaborating gynecologic oncologist or a member of the health care team or a review of medical records by the site Research Coordinator (RC). Potential subjects will be approached by the gynecologic oncologist, member of the health care team, or RC with study information and screen and consent the subject if they are interested either with a hard copy of the consent or with a REDCap consent on tablet, and the subject will also indicate availability for scheduled sessions and availability of technology resources. The research team will then follow up with a phone call to arrange for technical training. If the person is approached in person but wants more time to think about it, the research team can give study information to the patient and arrange to call or email the patient at another time to ascertain if the patient is interested in participation.

Alternately, potentially eligible individuals with upcoming clinic visits may be mailed or emailed a study brochure and an accompanying letter describing the study before their clinic visit, giving the potential subjects a phone number to call to opt out if they are not interested in the study. If they do not opt out, a member of the study team will call or email them to determine potential interest in the study. If they are not reached after 5 attempts, they may be approached in the clinic to discuss the study and to potentially consent and enroll.

B. Phone Recruitment from Clinical Sites.

In situations in which it is not feasible for the study team to consent the patient in the clinic, potentially eligible subjects will be approached by the gynecologic oncologist, member of the health care team, or a member of the study team with study information and asked for permission for the study team to contact them by phone or email. If verbal permission is provided, the patient name, email address, and phone number will be provided to the study team who will complete the screening and consent by phone or email. Because people are often reluctant to answer calls with phone numbers they do not recognize, the study team will be able to try up to 8 times to reach the potential subject, and will be able to leave up to 3 messages for a number to call back if the survivor is interested in the study, or 4 reminder emails. The patient may also be provided with the phone number or email address of the RC.

1B) As a supplement to in clinic recruitment, the study team will get a list of the ovarian cancer patients who have been treated in the last 5 years at the institution. These individuals will be mailed or emailed a study brochure and an accompanying letter describing the study and giving the potential subjects a phone number to call to opt out if they are not interested in the study. If they do not opt out, a member of the study team will call them to determine potential interest in the study. Because people are often reluctant to answer calls with phone numbers they do not recognize, the study team will be able to try up to 8 times to reach the potential subject, and will

be able to leave up to 3 messages for a number to call back if the survivor is interested in the study.

Additionally, the team at UMiami will work with the Florida Cancer Data System (FCDS) to obtain a list of potential participants meeting our study criteria. Identified participants from the FCDS will be mailed a packet including a patient contact letter and a patient response form and a letter from the Department of Health. If after 3 weeks from sending the initial packet there is no patient response, a second mailing will be sent with the addition of the telephone opt-out card. The telephone opt-out card explains to the patient if no response is received, the study investigator and/or a member of the study team will attempt to contact them via a telephone call, text, or email to introduce the study. If there is no response to the second mailing and the telephone opt-out card after 3 weeks, a telephone call will be attempted by the study staff. We will continue to use the established pre-screening and consent protocol for those participants who express an interest in our study (see below). For FCDS subjects the Miami team will use a Question and Answer Script (provided by the FCDS) that explains “how our study received their name”. Information obtained from the FCDS registry will be treated with the utmost security, all data will be stored in our UM secure servers and only study personnel will have access to this information.

In Path 2, ovarian cancer survivors will hear about the study from referring gynecologic oncologists (Alaska, Montana, GreenBay, WashU), from social media, Steps Through Ovarian Cancer, from other study subjects or contacts, and gynecologic oncologist colleagues of the research team. Survivors seen by referring gynecologic oncologists (Alaska, Montana, GreenBay, WashU), or gynecologic oncologist colleagues of the research team will be given or emailed an informational brochure about the study. They will also be able to see posters of Living WELL at the gynecologic oncologists’ offices. These brochures and posters contain contact information that the potential subject can use to contact the study team. They will be asked to contact the study coordinator at the Fred Hutch/University of Washington Cancer Consortium (if they are from Alaska, Montana or Green Bay), at Miami (if they are from Florida) or alternately the Coordinating and Data Core at UI (these and other locations) by phone or email if they are interested in participating, or alternately will give permission for a study team member to call them or email them to provide more information about the study. In addition to a phone number and email address for more information, the brochure and social media advertisements will contain a link to a REDCap prescreening questionnaire for potentially interested subjects to determine if they qualify. If they qualify for the study on the pre-screening questionnaire, the potential subject can enter their name and contact information and a member of the study team will contact the subject to confirm the screening, describe the study and answer questions about the study, and complete the informed consent if the individual is interested. The informed consent may be completed by REDCap or with an emailed or mailed copy using procedures described above.

Alternatively, at the end of the prescreening questionnaire, they will also be given a phone number and email address if they would like to contact the study team instead. If potential subjects email or call Fred Hutch/University of Washington Cancer Consortium (Alaska/Montana) or the Coordinating and Data Core at UI (other sites) for more information about the study or give permission for the UI to call them to provide more information, these potential subjects will be screened by phone by Coordinating and Data Core staff or Fred Hutch/University of Washington Cancer Consortium staff and consented following successful screening. Screening by phone utilizes self-report data and enrollment will be based upon self-report data. Patients who do not come from clinical sites will provide contact information for their gynecologic oncologist or oncologist as part of the consent process. Following the consent their physician(s) will be contacted to verify the self-report medical information. Information requested from the physician

will include most recent clinic notes, initial clinic and surgery note, and information about cancer diagnosis (stage, grade, tumor histology, extent of cytoreduction, completion of chemotherapy, current medication, CA125, significant past medical history). We anticipate that situations in which self-report data does not match physician data will be rare; however, in such situations, subjects continue in the group and sensitivity analyses will be performed. All study information including PHI will be collected in a secure REDCap interface housed at the UI.

## 6.2 Screening

Potential subjects will be screened for exclusion criteria. Screening for depression will use the CES-D[34,35]. The Center for Epidemiological Studies-Depression Scale (CES-D) is 20-item measure rating frequency of depressive symptoms over the past week. Scores of 24 or higher are associated with severe clinical depression and will be excluded.[34,35] The CES-D and its subscales have been strongly related to physiological variables in previous ovarian cancer research.[12] So that they can receive adequate attention, survivors with scores equal to or above 24 will not be included in groups. Instead, they will be mailed a list of resources that they can use to address their health concerns. If the study team has concerns about a subject's ability to understand English for participation in the intervention, the Wide Range Achievement Test (WRAT)[56] will be administered. Mental health history and current status and substance use will be abstracted from survivor medical records and will be included in screening questions. This screening will occur at the clinical sites for local survivors, will occur at Fred Hutch/University of Washington Cancer Consortium for survivors recruited from Alaska and Montana, and by Redcap screening interface or by phone at the Coordinating Core for survivors from elsewhere. It should be noted that because of time it may require to fill the various cohorts, time between screening and randomization may vary. It is possible that potential subjects may have recurred or gone on active chemotherapy before the start of the trial. This will be assessed in the initial assessment which is done within 1-2 weeks of the study. In the case of such a change, these individuals will still be allowed to participate in the intervention.

## 6.2 Randomization

Assignment to either ML or HL will be done by cluster-randomization stratified by time slot as follows. When subjects enroll, they will provide their availability for each of 3 time slots during which a group will be offered. Subjects will be assigned to a time slot for a web group cohort according to their availability, in the order of enrollment, with each cohort comprised of 5-8 subjects. Before randomization subjects will be re-contacted to confirm that they are still available. Once a time-slot cohort of 5-8 is filled, the cohort will be randomized to either ML or HL, drawn from the corresponding stratum. The cluster-randomization for each strata will employ permuted blocks of block size 2 or 4. To avoid a cluster having a majority of participants with recurrence an exception will be made for subjects with recurrence, such that if there are already 3 subjects with recurrence in the same web-group cohort, the subject will be assigned to the next cohort at that time slot. To minimize waiting time, when the first person recruited has been waiting 3 months of longer, the cohort may begin with at least 5 subjects. Randomization lists will be generated by the statistician prior to the enrollment of subjects and allocation will remain concealed until a group of 5-8 needs to be assigned. The randomization sequence will be stored in a password protected file via a password protection software interface. The Research Coordinator will be the only person with access to this file. When a group is complete and ready to start, to facilitate planning, the group will be randomized by the research coordinator accessing the file. Upon entering an ID code for that particular group an assignment will be shown for that group. Facilitators will be informed approximately 1-2 weeks in advance so that they can plan for the group. It should be noted that facilitators' knowledge of group assignment the week before the group starts will not bias subject recruitment because the slots will have already been filled for that group. Subjects

will learn their randomization via a letter sent through mail/email. Randomization should render equal representation of racial/ethnic, SES, and geographic backgrounds, and recurrence status but we will control for any baseline differences.

### 6.3 Study Activities

The following procedures refer to both arms of the intervention trial. Subjects will be given the option of using their own tablets, laptops, or desktops for the group conferencing, or a study-provided tablet (and headset if necessary) or webcam which will be mailed out to them if they need it. Tablets with wireless connectivity will be available for subjects who do not have internet connections available. Subjects will return the tablets or webcams when their study participation is completed. Groups will begin when a cohort of 8 subjects has been randomized. Groups may begin with 5-7 individuals if any participants have been waiting for longer than 2 months for their group to start. 2-3 cohorts of each arm of the study will be conducted simultaneously to accommodate different time preferences of subjects. Subjects will receive periodic reminders from the time of their consent to the beginning of their group about the total number of people enrolled in their respective group, and when they can approximately expect group activities to begin. In the unlikely circumstance that following randomization but before participation in Week 0 a participant has circumstances arise that prevent their participating in the group, the participant may be rescheduled to participate in a future group of the same randomized arm. However, if that rescheduling occurs more than a month following their initial completion of baseline surveys, they will be requested to complete their baseline surveys again before their new group starts.

Before beginning either arm of the intervention, subjects will receive a guide with a link to surveys, instructions for use of the website and videoconferencing, and will have individual training phone calls/zooms for using the website and web-interface conferencing with the study team at UI. The first training will take place before randomization, and the second post-randomization. When a cohort time slot has been filled, subjects will complete an initial assessment using a secure REDCap interface housed at UI and subsequently subjects will be randomized. Subjects will receive notification of their randomization via a letter sent through mail or email. They will then participate in a web-based introductory group informational session with members of their group (Mindful Living or Healthy Lifestyles). This gives subjects additional practice using web conferencing in a group setting and introduces the expectations and ground rules for the group. Subsequently, each subject will attend 10 group sessions lasting 1.5 to 2 hours via secure web-video conferencing. Number of log-ins, extent of meditation practice and daily reflections, and session attendance are assessed on the study website or through brief questions sent daily and securely through REDcap.

Subjects will participate for 12 months following randomization. There will be a booster session at approximately 4.5 and at 9-10 months post-randomization. After the 11 week session, research coordinators may contact participants over phone, by email, or by text to remind them of their booster sessions and surveys. There will be an assessment at following completion of the group (at approximately 3-months post-randomization), at 6-months and 12-months post-randomization. Participants will receive $20 for completing the assessment at 6-months and another $20 for completing the assessment at 12 months. There will be approximately a 30 day window on either side of these dates to account for potential scheduling issues.

If participants wish to contact other participants at the end of their participation in their respective group, they can do so by using the private chat function of Zoom. They can also contact the study after their groups have finished to share their contact information with other participants. Establishing contact with other participants at the end of a group's sessions is not a requirement

for this study. During their participation, participants will also receive a letter thanking them for their support and a gift tote-bag (Attached: Living Well 10 Week Thank You Letter). After the 11-week session, participants may also, if they wish, submit 5-10 minute testimonial videos or testimonial texts about their experience of the program which can be uploaded to the study website at (livingwellstudy.org) with the participant's permission, or shared on social media (Twitter, Facebook, Reddit, TikTok) with their permission. At successful completion of 12-month surveys, depending on which group participants are randomized to, they will either receive a USB containing recordings or a document containing summary of the information covered in the group they were not randomized to.

Recordings of missed sessions will be made available to people who miss a session. If participants miss a session and choose to view a recording of the missed session, they are not to share the contents of the recording with anyone so that the confidentiality of the other participants can be preserved. However, even if participants arrange a time and watch the recording for a missed session, that session will still count as missed, and they may not be able to continue if they miss more than 2 sessions. In the event that a participants misses a session, the group leader will have the option of calling the participant later in the week to check in and see if the participant has been able to keep up with study items.

Blood Spot Sub-study:
Blood spots will be collected before randomization of the intervention and again within 2 weeks following the end of the 11-week intervention. If subjects consent to this sub-study, they will be provided with two small kits that will contain a lancet to do the finger-prick, an alcohol swab for sterilizing their skin, cotton gauze for cleanup, a band aid, the blood spot collection card, and a pre-paid return envelope for sending the materials back. After subjects who have consented for the substudy receive their bloodspot kits, they can be contacted over the phone and walked through the process if necessary. They will be provided with reference materials on how to use items in the bloodspot kit. Subjects will then return the completed Blood Spot Card in the pre-paid envelope. They will also be contacted at the end of the group intervention and walked through the process a second time should this be considered necessary for their post group finger prick.

**TABLE 3. FLOW CHART OF STUDY TIME-POINTS**

| Procedures | Screening | Enrollment | Pre-Randomization | Randomization[d] | Pre-Group Activities | Week 1 | Week 2 | Week 3 | Week 4 | Week 5 | Week 6 | Week 7 | Week 8 | Week 9 | Week 10 | Week 11 | Week 12 | Week 19-20 | Week 26 | Week 39-40 | Week 52 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Screening | X | | | | | | | | | | | | | | | | | | | | |
| Informed consent | | X | | | | | | | | | | | | | | | | | | | |
| Demographics | | X | | | | | | | | | | | | | | | | | | | |
| Medical history[a] | X | X | | | | | | | | | | | | | | | | | | | |
| Assessments[b] | | | X | | | | | | | | | | | | | | X | | X | | X |
| Randomization[c] | | | | X | | | | | | | | | | | | | | | | | |
| Technical training | | | X | | X | | | | | | | | | | | | | | | | |
| Group introduction | | | | | | X | | | | | | | | | | | | | | | |
| Study intervention | | | | | | | X | X | X | X | X | X | X | X | X | X | | | | | |
| Booster sessions | | | | | | | | | | | | | | | | | | X | | X | |
| Adverse event review & evaluation | | | | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

a: Disease and treatment status
b: FACT-O, PSS, AAQ-II, BEAQ, FACIT-F, MOCS, CESD, POMS-SF, FMI, CWS, Brief COPE, SPS, PSQI, Godin, PHQ, demographics, COVID survey
c: See section 6.0 for randomization process
d. technical training and pre-group assessments may occur before or after randomization

## 6.4 Interventions

**Mindful Living Condition.** This is a behavioral web-conferenced group intervention teaching stress reduction, cognitive behavioral therapy (CBT), mindfulness strategies, acceptance and commitment strategies, communication, and other skills during an introductory session and 10 1.5-2 hour sessions facilitated by a clinical psychologist and a graduate student or postdoc.

**Table 4. Weekly Mindful Living Session Topics and Relaxation/Meditation Exercises**

| Wk | Session Topic | Exercises | Linkage to sample OC issues/ concerns |
|---|---|---|---|
| 1 | Stress response and stress management. Developing an awareness of personal stressors. Finding meaning and sources of personal strength | Progressive muscle relaxation (PMR) & breathing | High levels of stress, and uncertainty Disease/treatment related concerns (e.g., progression, symptom burden) |
| 2 | Cognitive Appraisal: Relationships between thoughts, emotions, and physical responses. | Passive PMR with guided imagery | Fear of recurrence/death, bodily changes, dreading the worst with any new symptoms |
| 3 | Cognitive Restructuring: Demonstration & discussion on alternative responses to negative self-talk. | Autogenic relaxation | Fear of recurrence, self-image; adjusting expectations; dealing with symptoms |
| 4 | ACT: Identification of avoidance and control strategies; finding effective alternatives through personal values, acceptance, and gratitude; using defusion to reduce emotional reactivity; overcoming avoidance | Introduction to Mindfulness, Guided mindful body scan | Fear of recurrence, living in the face of uncertainty in the future, abilities, work, meaning, creating a new normal, avoiding pain and anxiety |
| 5 | Coping strategies: problem-focused or emotion-focused coping strategies. Acceptance-based strategies for painful emotions; decreasing avoidance. | Mindfulness meditation | Coping with symptoms, coping with loss of abilities, work challenges, challenges of asking for help, self-nurturance |
| 6 | Social support: Benefits & types of support. Strategies for enhancing support and meaningful relationships. | Mindfulness meditation | Changes in relationships, loss of intimacy, avoiding conversations about symptoms, death, |

| | | | |
|---|---|---|---|
| **7** | Effective communication: Becoming aware of needs and communicating them effectively. | Mindfulness meditation | Expressing needs adaptively & asking for help; doctor-patient and intimate relationships |
| **8** | Anger management: Identifying patterns of anger expression and dealing with anger. | Loving kindness meditation | Interpersonal conflict, frustration with health care, assertiveness |
| **9** | ACT: Meaning and values: Discussion of personal values, spirituality, meaning in life with respect to cancer. Strategies to deepen meaning and enhance committed action. | Guided relaxation and visualization | Creating a meaningful life in the face of uncertainty, acceptance of a new normal |
| **10** | Wrap up: Review & assessing personal growth. Developing a maintenance plan with strategies for living more fully. | Guided relaxation and visualization | Generalizing skills to daily life, redefining roles, empowerment |

**Health Promotion (HL) Condition (*Healthy Lifestyles*).** This is a web-conferenced group intervention designed to provide relevant lifestyle information for ovarian cancer survivors. The HL arm will provide sessions on ovarian cancer survivorship and quality of life, exercise, nutrition, sleep, stress, cognition, body image, integrative medicine, and development of a lifestyle survivorship plan. There will be a group introductory session and 10 1.5-2 hour sessions facilitated by a health educator and a graduate student or postdoc.

**Table 5. Weekly Health Promotion Session Topics**

| Week | Session Topic | Linkage to sample OC concerns |
|---|---|---|
| 1 | Common Survivorship Issues | Understanding OC, importance of HRQOL |
| 2 | New Directions in Ovarian Cancer Treatment | Understanding new treatment options |
| 3 | Exercise and Cancer Survivorship | Benefits/ challenges of remaining active |
| 4 | Nutrition and Cancer Survivorship | Appetite changes, adequate nutrition in cancer care |
| 5 | Sleep | Healthy sleep maintenance; improving sleep |
| 6 | Stress and Health | Importance of stress and stress reduction |
| 7 | Cognition, Aging, and Chemo-Brain | Cognitive symptoms & memory challenges |
| 8 | Body Image and Sexuality | intimacy and relationships; role changes |
| 9 | Integrative Medicine | Finding reliable information on integrative care |
| 10 | Wrap-up: Developing a Survivorship plan | Advance planning; survivorship care |

## Stopping points

Criteria for suspending or terminating the study would be if during the study there is a perceived danger for subjects due to participation. This is not anticipated. However, if during interim analysis we find that more than 25% of subjects in the Mindful Living arm move from a non-depressed state (CESD < 24) to a depressed state (CESD ≥24) we would evaluate whether the trial should be stopped..

## 6.5. Risks

Based on our previous work, this study as described is of minimal risk. Minimal risk is defined as the probability and magnitude of harm or discomfort anticipated in the research not greater than that ordinarily encountered in daily life or during routine physical or psychological exam.

During the psychosocial questionnaire administration, there are minimal potential emotional risks to subjects due to the somewhat personal nature of the questions asked regarding mood and quality of life. Answering the questions may make subjects upset or uncomfortable; subjects will be informed that they can choose not to answer questions they do not wish to answer.

During the group conferencing sessions, sensitive topics may be discussed; subjects are free to participate as much or as little as they feel comfortable.

There is a potential loss of confidentiality from the web conferencing format; all subjects will be instructed in confidentiality practices at the beginning of the groups (see below).

**Risks of Immune Response Sub-Study**
Slight discomfort or stinging sensation when using the lancet.
Small risk of infection and/or bruising.

## What Is Done To Minimize The Risks

Because interactions will be in a group setting, in the first session subjects will be instructed about the importance of confidentiality. They will be required to access the web-based intervention in a private location where others could not overhear the group conversation. Additionally, subjects can choose to disclose as much or as little personal information as they feel comfortable with in the group. Confidentiality of subject information will be strictly preserved, and subject names will not be revealed in publications or reports.

Subjects will be informed that they may withdraw from the study at any time, with no penalty, should this occur; conversely, we will attempt to resolve any problems causing these responses, should survivors wish to continue participating. If a participant experiences an adverse or unanticipated event during the study, research staff in contact with that participant will notify the lead investigator at each participating site or at UI if the participant is not being followed at one of the participating clinical sites. Subjects will be asked to report any new health problems that arise in connection with the study to the study coordinator at their site or to the Coordinating and Data Core at the UI if they are not from a participating clinical site. He/she will refer the survivor to their physician for serious health problems. Should a survivor disclose high levels of emotional distress (e.g. levels of depression consistent with a diagnosis of depression [CESD > 24] ) during the study period, designated study personnel will contact the participant to offer appropriate resources as determined by the lead investigators. Documentation of appropriate resources offered to the survivor and of the survivor's acceptance or rejection of the resources will be made by the Coordinating and Data Core.

Study data will be collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools supported by the Biomedical Informatics group in the UI Institute for Clinical and Translational Science. REDCap (www.project-redcap.org) is a secure, web-based application with controlled access designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless downloads to common statistical packages; and 4) procedures for importing data from external sources. For multi-center studies REDCap uses Data Access Groups (DAGs) to ensure that personnel at each institution are blinded to the data from other institutions Each study team member will be granted access to REDCap through a secure login by the study PI, study manager or their proxy. REDCap supports Two-factor authentication using DUO.

Risks of Immune Marker Sub-Study:
For Risks of Immune Response Sub-Study: The process and products in the kit are used routinely in a wide range of healthcare applications, including measurement of blood glucose (blood sugar) in diabetes. The equipment is sterile and following the instructions provided in the kit (like cleaning the area) will minimize infection risk.

## 6.6. Benefits

There may or may not be benefits to subjects in the study, however, risks are minimal. Subjects have the possibility of learning useful information about stress management, meditation, and

health promotion that may provide benefit to them. The results of the study may support efficacy of an intervention that may improve health related quality of life and decrease distress among ovarian cancer survivors. Moreover, this study will allow ovarian cancer survivors to connect with each other independent of rural/urban residence without the need for travel. Thus, we believe that the risks are reasonable in relation to the anticipated benefits.

### 6.7. Potential benefits to society in terms of knowledge to be gained

This study addresses an unmet need in ovarian cancer survivors- that is a group psychosocial intervention to address distress and/or to provide information about healthy lifestyle practices that are relevant to ovarian cancer. Our ultimate goal is to substantially improve outcomes in an understudied group of cancer survivors (ovarian cancer) with a high level of mortality by developing actionable strategies to address modifiable psychosocial factors to improve health related quality of life. Thus, this work is of great clinical and public health significance.

## 7. Statistical Evaluation/Considerations

Descriptive statistics will be computed for all demographic and baseline variables for each of the treatment arms and distributions of continuous variables will be evaluated for normality. If data are non-normal, appropriate transformation will be applied or non-parametric methods may be used. Demographic and baseline variables will be compared between treatment groups using t-test for continuous variables, Wilcoxon-rank sum test for ordinal, and non-normally distributed continuous variables, and Pearson Chi-square test for categorical variables. Variables found to differ significantly between the groups will be used as covariates in the comparison of outcome measures between the treatment groups. A number of variables known to influence our primary outcomes (e.g., income, education, marital status, and race/ethnicity) will be considered as possible covariates. These putative control measures will be analyzed as covariates if they are correlated with our outcomes (at $p<.10$). The internal consistency (coefficient alpha) and test-retest correlations over the course of data collection will be evaluated for multi-item inventories. While every effort will be made to follow-up with subjects, it is expected that approximately 25% of the subjects may be lost across the study period. Intent to Treat (ITT) analysis will be performed using all available data for all randomized subjects. Reasons for subject drop-out will be recorded and compared between treatment groups. Subject characteristics and outcome measures collected prior to drop-out will be compared to those that complete the study follow-up. In the presence of missing data, under the assumption of missing at random (MAR), linear mixed model analysis, which can handle incompletely observed subjects and uses a likelihood estimation method, will provide correct likelihoods and lead to valid estimates. However, since the data under analysis cannot distinguish if data is MAR or if it is missing not at random (MNAR), sensitivity analysis will also be performed using pattern mixture models. Multiple imputation will be used for sensitivity analysis by imputing from a non-random pattern mixture model. Per protocol analyses will be performed including participants that attended at least 6 sessions of their respective intervention condition and completed the immediate post-intervention surveys or any subsequent follow-up surveys.

Aim 1 tests whether the Mindful Living vs. HL intervention increases HRQOL, and decreases in perceived stress (primary), and decreases anxiety, depressive mood, and fatigue (secondary) during a 11-week intervention, and whether changes are sustained over a 12-month follow-up. Based on preliminary data, there will be a detectable differences in mean immediate (post-treatment) change from baseline and in mean sustained change (6 and 12 month) from baseline, for the primary and secondary outcome measures between the ML and the HL arms with an anticipated final sample size of 192 subjects. The detectable group mean difference was calculated for a two-tailed test at the 0.05 significance level with 0.80 power for a final sample

size of 96 subjects per treatment arm for a cluster-randomized design with corresponding intracluster correlation coefficient (ICC) estimated from our pilot data. The 96 subjects are from 16 web-groups (cohorts) per arm with an average of 6 subjects per cohort. This assumes 25% dropout, so that a total of 256 subjects will be enrolled, comprised of 32 cohorts, with 8 subjects per cohort, that will be randomized to one of the two treatment arms. Based on the calculations below we anticipate that our sample size and the variability in our data will enable us to detect smaller intervention effects than those observed in our pilot for our primary variables and for several of our secondary variables for Aims 1 and 2. The effect sizes we anticipate being able to detect are consistent with the medium effect sizes generally observed in other studies of psychosocial interventions in cancer survivors.

**Table 6. Power Considerations**

| | **SD** | | **Detectable difference (effect size=diff/pooled SD)** | | | **Between Group Difference in Immediate Change (from pilot)** | |
|---|---|---|---|---|---|---|---|
| **Outcome Variables Aim 1** | **Between Subject** | **Residual** | **ICC** | **Immediate (Post-tx)** | **Sustained (6 and 12 mo.)** | **Observed Mean (effect size)** | **95% CI** |
| **FACT-Total** | 13.6 | 9.3 | 0.010 | 5.5 (0.19) | 6.1 (0.46) | 9.1 (0.69) | (-3.7, 22.0) |
| **PSS** | 7.1 | 4.2 | 0.010 | 2.5 (0.29) | 2.8 (0.47) | -6.7 (-1.13) | (-12.6, -0.9) |
| **CESD** | 7.6 | 5.3 | 0.150 | 4.1 (0.34) | 4.5 (0.60) | -5.8 (-0.77) | (-13.0, 1.5) |
| POMS-anxiety | 4.1 | 2.9 | 0.078 | 2.0 (0.49) | 2.2 (0.54) | -2.0 (-0.49) | (-6.0, 1.9) |
| POMS-fatigue | 4.6 | 2.9 | 0.204 | 2.4 (0.59) | 2.7 (0.66) | -2.0 (-0.49) | (-5.9, 1.9) |
| **AIM 2** | | | | | | | |
| **MOCS relaxation** | 1.4 | 1.2 | 0.125 | 0.9 (0.53) | 1.0 (0.59) | 3.0 (1.77) | (1.0, 5.0) |
| **MOCS coping** | 4.1 | 1.8 | 0.010 | 1.1 (0.43) | 1.2 (0.47) | 3.8 (1.49) | (0.7, 6.9) |
| **FMI** | 7.4 | 3.5 | 0.010 | 2.1 (0.42) | 2.3 (0.46) | 3.5 (0.71) | (-1.7, 8.8) |
| **AAQ** | 2.8 | 2.5 | 0.284 | 2.3 (0.65) | 2.5 (0.71) | -2.7 (-0.76) | (-6.3, 1.0) |

## 7.1. Statistical analyses for Aim 1

Aim 1 will be tested using linear mixed model (LMM) analyses for repeated measures with treatment group (ML vs. HL), time, and treatment*time interaction as fixed effects. Random effects include web group cohort (within treatment) and subjects (within cohort, within treatment). In fitting the LMM, appropriate covariance structures for the longitudinal measures within subject will be considered, such as compound symmetry, or heterogeneous compound symmetry, and then selected based on Akaike Information Criteria (AIC) and Schwarz's Bayesian Information Criteria (BIC). Specifically, to test for immediate change (post-intervention), the linear mixed model analysis will include the baseline and immediate post-intervention timepoints. The difference in immediate change post-treatment between the different conditions will be tested by the interaction effect. For the mixed model analysis of long-term change, data from all 4 timepoints will be used in fitting the model, with the difference in long-term change at 6 and 12 months assessed using tests of mean contrast. Bonferroni adjustment will be applied to the *p*-value to test for long-term change at 6 and 12 months. For each of the two analyses, if confounding variables are found to differ between the treatment groups such that covariate adjustment is necessary, a secondary comparison of the primary outcome variable between treatment groups will be made by expanding the LMM to include covariates. These variables may include age, education, income, race/ethnicity, geographic location, recurrence, maintenance chemotherapy, recurrence during the study period, and disease stage. Statistical significance for efficacy of ML vs. HL will be based on a two-tailed test at the 0.05 significance level with treatment effect

summarized as mean difference with 95% confidence interval. Similar analyses will be performed for the secondary outcome measures.

### 7.2. Statistical analyses for Aim 2

The statistical analyses for Aim 2 will examine potential mediators of any observed intervention effects on outcome measures, with examination of skills that support post-intervention and sustained skills. For Hypothesis 2A effects of the intervention on relaxation, coping, mindfulness and acceptance outcomes, the analytic plan will be similar to those in Aim 1, with similar targeted effect sizes and similar power projections. For Hypothesis 2b, testing mediation of intervention effects, mediation analysis will explore the causal pathway between intervention (ML and HL) and changes in primary outcomes (HRQOL, depressed mood, and perceived stress) and secondary outcomes (anxiety and fatigue) from baseline to post-intervention (immediate) and from baseline to 12 months (sustained) with change in reported relaxation, mindfulness, acceptance, and cognitive coping skills as mediators. With the independent variable X (intervention) randomized to web-group cohorts, and the mediator variables M (change in mastery in relaxation, mindfulness, avoidance, and cognitive coping skills), and the dependent variable Y (change in HRQOL, depressive mood, stress, and secondary variables) measured at the subject level within cohorts, we have a two-level hierarchy with a 2-1-1 design. For this multilevel design, multilevel structural equation modeling (MSEM) will be used to estimate and test the direct and indirect effects to assess multilevel mediation[57] using SEM or GSEM in Stata or MPLUS.

Power for Hypothesis 2B is based on the pilot data where large effects of group assignment (ML vs. HL) were observed on changes in potential mediators (relaxation, coping skills, mindfulness, and acceptance; range of d = .70-1.7). In the proposed model multilevel mediation framework this effect will include some variance attributable to the cohort to which the subject is randomized within the treatment arm, as well as the effect of the treatment itself, the latter of which is the effect of interest. We therefore conservatively estimate the true treatment effect for the mediators to be d = .60, representing the first arm of the mediation pathway. The second arm of the mediation pathway reflects the association between change in the mediators (relaxation, coping, mindfulness, and acceptance) and change in the outcomes of interest (HRQOL, stress, etc.) In our pilot work shown above, the absolute correlation values between these change variables ranged from .41-.76, corresponding to a d range of .89-2.3,[58] and we conservatively adopt this lower estimate (.89) for purposes of estimating power. Here we use the Monte Carlo approach for evaluating indirect (mediation) effects with 5000 replications and two Monte Carlo draws per repetition and an attrition-adjusted sample size of 192 (96 per group).[59] This produces power in excess of .99 for calculating significant mediated effects with a 95% confidence interval. In the event that the true effect sizes are substantially smaller (i.e., d=0.4 rather than .6 for the first path, and d = .6 rather than .89 for the second path) we will still have .80 power to detect significant mediated (indirect) effects.

### 7.3. Statistical Analyses for Aim 3

Aim 3, an exploratory aim, provides the opportunity to determine whether the effect of the intervention varies as a function of moderators such as rural residence, age, and specific clinical characteristics. For example, it is possible that subjects in rural areas might benefit more from the intervention because they have less access to connections with other survivors and health care information. Survivors who are closer to diagnosis or those who have not recurred may have more interest in acquiring information and skills that will assist them in negotiating their survivorship. Alternatively, survivors who are farther from diagnosis may have had more experience negotiating survivorship issues and may be more open to receiving new skills. Survivors who have recurred may be more highly motivated to develop new skills and acquire new information. As this Aim is

exploratory there are no directional hypotheses. The purpose of this Aim is to provide data for future research with this program to determine whether there are specific individual characteristics that make them more or less likely to benefit from the intervention. As an exploratory aim, Aim 3 is not powered for definitive results but to examine possible trends. To test Hypothesis 3, the LMM analyses described for Aim 1 will be expanded to include one of the factors of interest (rural vs. urban residence, recurrence (0,1), disease severity (early vs. advanced-stage), or time since diagnosis), age (< 65; >65). The model will include the factor as a main effect, and interaction effects with treatment and time (i.e. factor*treatment, factor*time, and factor*treatment*time). If any interaction effect is found to be statistically significant, specific tests of mean contrast will be performed to assess for intervention effect by the factor subgroups, with appropriate Bonferroni adjustment applied to the p-values to account for the number of tests.

### 7.4. Missing Data

While every effort will be made to follow-up with subjects, it is expected that approximately 25% of the subjects may be lost at follow-up. Reasons for subject drop-out will be recorded and compared between treatment groups. Participant characteristics and outcome measures collected prior to drop-out will be compared between those that drop out and those that complete the study. In the presence of missing data, under the assumption of missing at random (MAR), linear mixed model analysis which can handle incompletely observed subjects and uses a likelihood estimation method will provide correct likelihoods and lead to valid estimates. However, since the data under analysis cannot distinguish if data is MAR or it is missing not at random (MNAR), sensitivity analysis will also be performed following approaches recommended by Molenberghs and Kenward.[60] Methods for sensitivity analysis such as marginal delta adjustment, conditional delta adjustment, reference-based controlled imputation, and pattern mixture models will be considered. Nonnormality will be assessed, and if needed, variables will be transformed to approximate normality before imputation and retransformed back to original scale values. To avoid imputation bias, all variables in the substantive analyses and, if feasible, all variables predictive of the missing values (i.e. immediate post and 6 month response of the outcome measure, if available) or variables influencing the cause of missing data will be included. These multiple imputation analyses will be conducted using SAS PROC MI and SAS PROC MIANALYZE.

## 8. Data Collection and Record Keeping

The study will be administered by the lead institution, University of Iowa (UI). It will be monitored by a single Institutional Review Board at UI, which will set up reliance agreements with the Fred Hutch/University of Washington Cancer Consortium and UM IRBs. Each of the sites will be responsible for the screening, recruitment, enrollment, and support of assessment completion of subjects recruited at their respective institutions. The Coordinating and Data Core at UI will develop standardized operating procedures for regulatory and protocol compliance for all 3 clinical sites (UM, Fred Hutch/University of Washington Cancer Consortium, and UI) and for all study activities and data collection.

### 8.1 Collection and Storage of Data

REDCap data management software will be used to organize all data including documentation of informed consent, self-report measures, and clinical data. REDCap is supported at UI by NIH CTSA awards. All study information including PHI will be collected in a secure RedCap interface housed at the UI. Self-report measures will be collected after study enrollment. Subjects will be provided with a computer link and instructions for completion of surveys from home during the

week prior to the beginning of the group. Clinical data will be extracted from the medical record by study team members. Intervention website usage will be extracted from the administrator page by study team members.

There may be situations in which subjects would prefer to complete surveys using hard copies. In this situation, hard copy data will be hand entered into RedCap by study team members. When entering subject data, research assistants are only aware of the individual's subject number for the study. All materials are labeled with subject ID and not labeled with any other identifying information (medical record number or name). RedCap data identified only by subject ID may be downloaded into SPSS files kept on password protected servers in the Department of Psychological and Brain Sciences. These password protected files are only available to team members who have set up access through Information Technology Systems (Trent Petersen). Electronic data is stored only on these servers. The exception is that data which is being statistically analyzed by the PI or project statisticians is on password protected computers.

## 8.2. Screening Log

Information collected will include an individual's address, phone number and e-mail address, subject number and reason for not enrolling e.g., exclusion, lack of interest, currently excluded but may be eligible in the future. Women who are screened that do not enroll may subsequently be able to participate. For example, this would apply to individuals currently finishing chemotherapy who will be eligible when they complete it or to survivors whose availability does not fit the timing of the current group but will fit the timing of the next group being offered. The screening log will be kept so that these individuals can be called back when they either become eligible or a group is being offered that would work for them.

## 8.3. How Long Are Records Kept

For survivors who are eligible and approached but decline participation, their identifiers will be kept until the end of enrollment and then destroyed to make sure we do not contact them again. Similarly, for survivors who are ineligible, their identifiers will be kept until the end of enrollment to avoid their being evaluated again. They will be destroyed at 3 years post-chemotherapy or the end of the study whichever comes first. Information of subjects that are temporarily ineligible but may become eligible following the end of treatment or involvement in another study will be kept until the end of enrollment. Study records will be kept for 10 years after the close of the study to allow for complete data analysis of primary endpoints as well as moderators, mediators, and other information. Enrolled subjects who have indicated that we may contact them for future research studies will have their contact information kept for 10 years following the study.

For any study in which Iowa is the lead site, the Holden Comprehensive Cancer Center's (HCCC) Data Safety Monitoring Committee(DSMC) will be the DSMB of record. If the participating sites will be performing any onsite monitoring or auditing activities during the course of the study, any resulting reports should be sent to HCCC's DSMC. It will have oversight of overall data and safety monitoring for all sites. The level of DSMC monitoring and oversight is dependent on the risk level assigned to the protocol at the time of initial PRMC/DSMC review. Basic requirements entail subject registration in OnCore, documentation of adverse events and protocol deviations, and annual review by the DSMC. Regardless of risk level, all studies are required to have data collection forms developed in OnCore (eCRFs) to facilitate data and safety review by the DSMC. The Holden Comprehensive Cancer Center has a protocol development coordinator who is available to assist investigators with their protocol documents. This person serves as a point of contact between PIs, regulatory, and clinical staff to ensure the document includes all the necessary components prior to committee review. There also is an eCRF developer who works

with investigators and staff to ensure data collection forms meet all the necessary requirements. The complete Data and Safety Monitoring Plan is attached.

## 9. References


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# 10. Appendix

## 10.1 DATA AND SAFETY MONITORING PLAN

**Type of Clinical Trial:**

- ☑ Investigator-initiated (UI/HCCC)
- ❑ Investigator-initiated, participating site
- ❑ Pilot study
- ❑ Phase I
- ❑ Phase I/II
- ☑ Phase II
- ❑ Phase III
- ❑ Compassionate-use/Expanded Access
- ❑ Interventional Treatment
- ☑ Interventional Non-Treatment
- ❑ Non-Interventional

**Study risk-level:**

- ❑ Level 1—low risk of morbidity or death, * <1% of death or any adverse event
- ☑ Level 2—risk of death* <1% or any adverse event 1% – 5%
- ❑ Level 3—risk of death* 1% – 5% or grade 4 – 5 SAE 1% – 5%
- ❑ Level 4—risk of death* >5% or grade 4 – 5 SAE >5%
- ❑ Drugs being used on a "compassionate" basis

***** *Risk of death" refers specifically to 100-day treatment-related mortality*

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**Reporting and Monitoring Requirements:**

All institutional investigator initiated trials (IITs), regardless of assigned risk level are subject to routine DSMC monitoring activities which may include but are not limited to review of signed consent documents, eligibility and adverse event reporting.

All institutional IITs have the following **reporting requirements** as part of their DSMP:

- Register all subjects in HCCC's Clinical Trial Management System, OnCore
- Document Adverse Events
- Document protocol deviations
- Provide an annual progress report to the DSMC via OnCore data export

**Selected monitoring strategy based on risk-level:**

**Risk Level 2**

Interventional trials with a risk of death* (<1% or any adverse event 1% – 5%), e.g. behavioral interventions, nutritional therapies, low risk procedures (e.g., endoscopy, glucose-tolerance tests, induced sputum, skin or muscle biopsy, nasal wash, lumbar puncture, bone marrow biopsy,

imaging requiring sedation), as well as therapeutic trials involving agents with known safety profiles already licensed for the indication and age group. Most disease-prevention trials will be considered at least a Risk Level 2.

Study Safety Review

The PI or designated study personnel will review all study data for completeness.

Additional Reporting Requirements

- Serious adverse events will be entered directly into an OnCore SAE report by the research team. OnCore will send an automatic notification to the DSMC Chair/acting Chair and staff for review.

**Routine Adverse Event Reporting**

For non-serious Adverse Events, documentation must begin from the first day of study intervention and continue through the 30 day follow-up period after the study intervention is discontinued**.**

Collected information should be recorded in the electronic/Case Report Forms (eCRF/CRF) for that subject. A description of the event, its severity or toxicity grade (according to NCI's Common Toxicity Criteria (CTCAE 5.0)), onset and resolved dates (if applicable), and the relationship to the study drug should be included. Documentation should occur in real time. The principal investigator has final responsibility for determining the attribution of the event as it is related to the study drug.

**Serious Adverse Event Reporting**

For any experience or condition that meets the definition of a serious adverse event (SAE), recording of the event must begin after signing of the informed consent and continue through the 30 day follow-up period after treatment is discontinued.

Investigators must report to the DSMC any serious adverse events (SAE), whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64). SAEs must be reported via an OnCore SAE Report within 24 hours of learning of the event.
An adverse event is considered **serious** if it results in ANY of the following outcomes:

1. Death
2. A life-threatening adverse event
3. An adverse event that results in inpatient hospitalization OR prolongation of existing hospitalization for ≥ 24 hours
4. A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5. A congenital anomaly/birth defect.
6. Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to

prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

**Data Monitoring and Management**

*Subject Registration*

All studies that undergo PRMC review and/or utilize HCCC Clinical Research Services (CRS) resources are required to register subjects in OnCore. Each subject registration includes the following:

- The subject's IRB approved (version date) consent form and the date of their consent.
- Date of eligibility and eligibility status (eligible, not eligible)
- On study date and subject's disease site (and histology if applicable)
- On treatment date (if applicable)

All subject registration information is expected to be entered into OnCore within **2 (two) business days** after the subject's study visit.

*Subject Data*

For HCCC investigator initiated trials, research staff are responsible for entering subject study data (data collection) into OnCore electronic case report forms (eCRFs). These eCRFs must be approved by the PI and statistician prior to study activation to ensure sufficient and necessary data acquisition. All information entered into eCRFs will be traceable to the source documents which are generally maintained in the subject's file.

eCRF data entry needs to be timely and should be entered into OnCore as soon as possible but no later than **14 (fourteen) business days** after the subject's visit, including adverse events, tumor measurements, administration of study medication, concomitant medications, labs, and vitals. Physical exam assessments must be entered no later than **14 (fourteen) business days** following completion of the physician's clinic note in the medical record.

Timely data entry facilitates remote monitoring of data, allows the data to progress appropriately through the data cleaning process, and helps prevent a backlog of data queries.

*Forms Monitoring*

OnCore eCRF data are monitored on a routine basis (dependent on accrual) to ensure all data are entered completely, accurately, and within time requirements outlined above. The assigned DSMC monitor will coordinate and complete the data monitoring review. When the time comes to monitor a study (based on patient accrual and assigned risk level of trial) the monitor arranges for a selection of cases to be reviewed from among the subjects registered in OnCore. As part of the forms monitoring process, the assigned monitor will issue queries via OnCore (linked to the eCRF) to resolve missing, incomplete, and/or incorrect information. A member of the research team is expected to respond to these monitoring queries within **14 (fourteen) business days**.

The monitoring process can often identify misunderstandings or deficiencies in the written, research protocol requirements earlier in the study process and thereby improve data quality and reduce rework.

*Final Reports*

A summary of each subject's data record is continually available to the PI, research staff, and DSMC from OnCore's Biostat Console. The availability of this information is a valuable tool for the preparation of final reports and manuscripts as well as ongoing deficiency reports.

Antoni, M. H., et al. (2006). "How stress management improves quality of life after treatment for breast cancer." J Consult Clin Psychol **74**: 1143-1152.