REVITALIZE: *A Telehealth Intervention for Women with Advanced Ovarian Cancer and PARP Inhibitor-Related Fatigue*

PROTOCOL TITLE: REVITALIZE: A Telehealth Intervention for Women with Advanced Ovarian Cancer and PARP Inhibitor-Related Fatigue

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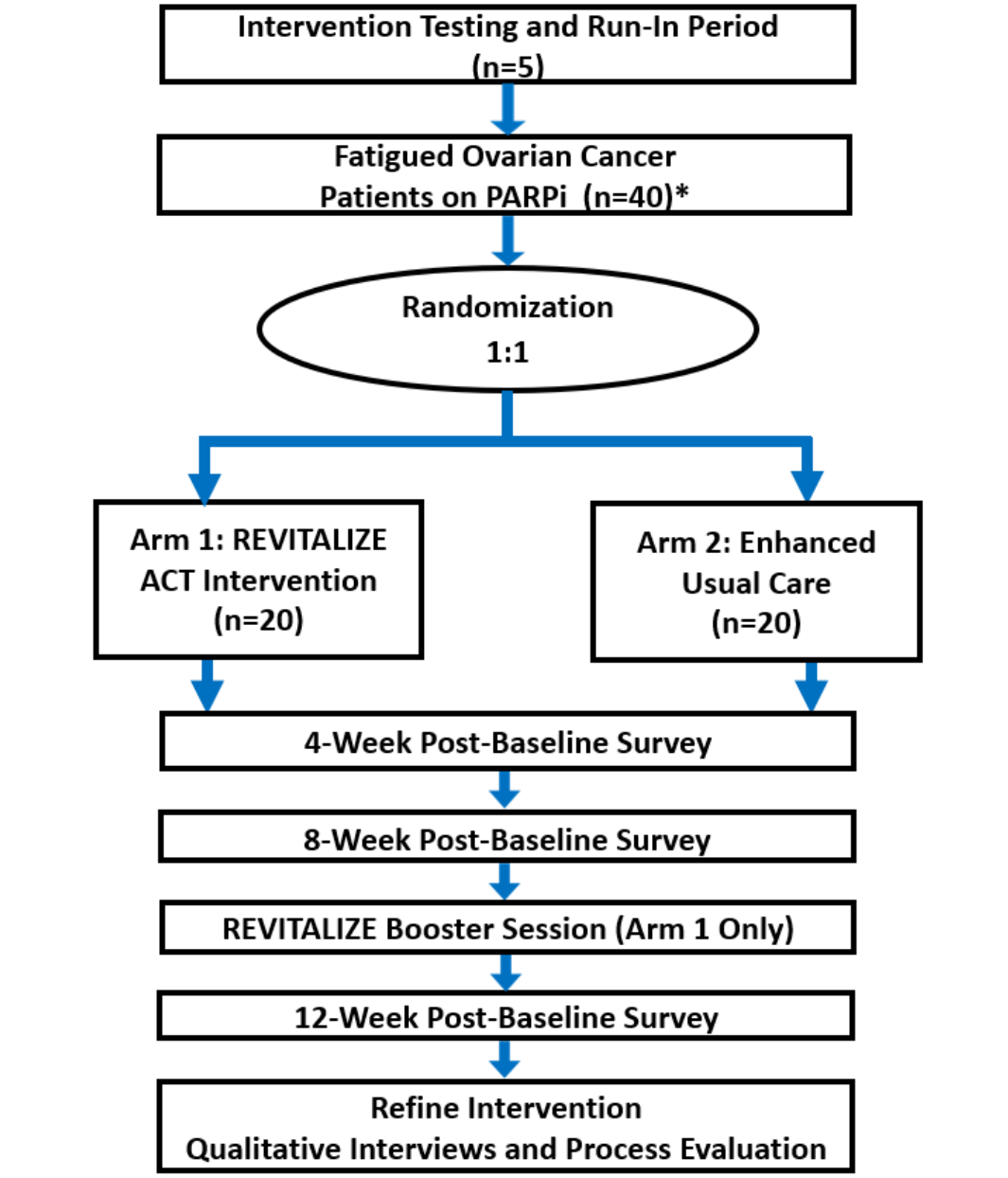
1.0 Protocol Schema



*** Overall enrollment may be higher to ensure 40 evaluable participants**

2.0 Objectives

Our long-term goal is to develop an effective and scalable intervention to reduce fatigue and symptom-related suffering in women with advanced ovarian cancer on PARP inhibitors (PARPi). In this study, we propose a two-arm, multicenter pilot randomized controlled trial to compare the feasibility, acceptability, and preliminary efficacy of REVITALIZE, a 6-week Acceptance and Commitment Therapy (ACT) telehealth intervention vs. enhanced usual care (EUC) in up to 50 fatigued patients with ovarian cancer on maintenance PARPi. Designed to increase psychological flexibility and values-based behavior, we hypothesize that REVITALIZE will improve psychological flexibility and fatigue-related interference and reduce fatigue, psychological distress, and fear of cancer recurrence, while improving overall quality of life (QOL). Collaborating across three academic cancer centers, our Specific Aims are to:

Aim 1: To assess the feasibility and acceptability of REVITALIZE in women with advanced ovarian cancer who experience PARPi-related fatigue. After pre-piloting the REVITALIZE intervention in a sample of up to 5 patients at the Dana-Farber Cancer Institute to test and refine the newly developed intervention, we will randomize up to 50 fatigued patients with ovarian cancer on maintenance PARPi to a 6-week ACT intervention vs. enhanced usual care (educational materials). **Feasibility** will be defined as ≥50% approach-to-enrollment rate of eligible participants and ≥70% completion of 3-month outcome assessments. **Acceptability** will be defined ≤20% withdrawing from the study overall, and ≤20% of participants on the intervention arm reporting high study burden.

Aim 2: To explore the effects of REVITALIZE on fatigue, emotional distress, fear of cancer recurrence, quality of life, and adherence in up to 50 women with advanced ovarian cancer on PARPi. We expect that REVITALIZE will improve psychological flexibility and
fatigue-related interference reducing fatigue (primary outcome), psychological distress, and fear of cancer recurrence, while improving overall QOL (secondary outcomes), compared to enhanced usual care.

3.0 Background and Rationale

3.1 Background

Oral PARPi have dramatically changed the treatment landscape for women with advanced ovarian cancer, but are poorly tolerated in a subset of patients. PARPi have been shown to improve progression-free survival in women with and without BRCA mutations (BRCAm and BRCAwt)[1], and are FDA approved for maintenance after first-line treatment of women with ovarian cancer, platinum-sensitive recurrent ovarian cancer,[2, 3] and treatment of recurrent ovarian cancer after three lines of treatment.[4] While PARPi have fewer side effects

than chemotherapy, many women cannot tolerate PARPi due to fatigue or nausea.[1] In clinical trials of PARPi, 18% of patients experienced moderate fatigue, and nearly 10% had severe to disabling fatigue.[5] Yet, the prevalence of PARPi-related fatigue is likely higher than documented because clinical trials rely upon clinician-reported symptoms, single-item measures to assess fatigue, or exclude grade 1 levels of fatigue in QOL analyses.[6, 7] Despite the many benefits that PARPi offer, many patients cannot tolerate treatment due to fatigue, which may impact adherence, treatment discontinuation, and ultimately progression-free survival.

Cancer-related fatigue is one of the most common and distressing symptoms reported by patients with ovarian cancer[8]. Fatigue compromises QOL, resulting in substantial physical, psychosocial, and economic losses for both patients and caregivers.[9] The National Cancer Institute has designated cancer-related fatigue a high-priority research area,[10] and national guidelines recommend routine screening for cancer-related fatigue and treatment with psychological or exercise interventions.[11] In prior work, we have demonstrated that more than 40% of women with ovarian and endometrial cancer in remission have clinically-significant fatigue one year after diagnosis.[12] In another study, we demonstrated that 25% of patients on oral chemotherapy have moderate-severe fatigue,[13] and these patients experience more anxiety and depressive symptoms, compared with patients without fatigue, as well as decreased physical functioning. To our knowledge, however, researchers have not specifically examined the prevalence of cancer-related fatigue in women with ovarian cancer on PARPi outside of clinical trials, or tested interventions to reduce fatigue in this population.

Our qualitative research in women with advanced ovarian cancer demonstrates that PARPi-related fatigue is associated with significant symptom-related suffering and functional interference. Recently, we conducted 21 in-depth interviews with fatigued patients with advanced ovarian cancer on PARPi (18-315, PI: Wright). While patients described their symptoms as milder than intravenous chemotherapy, they noted that fatigue insidiously limited their daily activities, interfering with their desire to participate in social events, physical activity, and work. One patient retired because she could not balance the PARPi- associated fatigue with her employment. Others reported the need for dose-reductions, treatment holidays, or changes in PARPi because of fatigue. Although most patients wanted to continue on PARPi, many reported difficulty coping, which evoked psychological distress and fears of cancer recurrence. All participants endorsed the importance of developing an ovarian cancer-specific intervention and indicated a preference for telehealth over clinic-based delivery. Interventions that reduce PARPi-related fatigue may increase treatment tolerability, enabling more patients to remain on treatment.

CBT vs. ACT for treating cancer-related fatigue

Cognitive behavioral therapy (CBT) is a highly effective, yet under-utilized, treatment for cancer- and treatment-related fatigue. The American Society of Clinical Oncology recommends CBT to address fatigue in cancer survivors.[11] Research has shown that CBT is effective in

reducing fatigue in patients with advanced cancer receiving palliative chemotherapy.[14-16] In a multi-center study, Poort (MPI) demonstrated that CBT significantly reduced fatigue and improved QOL, compared with usual care, with effects sustained for 3-months post-intervention.[17] However, only 5% of the participants had ovarian cancer; thus, it is unclear whether CBT is efficacious in this population. Moreover, 76/210 (36%) of eligible patients declined study participation because the required clinic visits were too burdensome.

Acceptance and Commitment Therapy (ACT) is another promising approach for treating fatigue, specifically in patients with ovarian cancer. ACT promotes actively facing and accepting distress and choosing life directions that reflect one's values, enabling patients to address multiple concomitant problems simultaneously (e.g. fatigue, depression, anxiety, and pain).[18] While CBT typically focuses on addressing one problem (e.g. fatigue), ACT targets the functional underpinnings that are common to multiple psychological and behavioral problems. ACT helps individuals to clarify who and what are most important to them (their values) to increase their ability to align their daily behavior with their values even in the presence of distressing thoughts, feelings, and physical sensations (e.g., fatigue, pain).[19] Instead of struggling to avoid fatigue (and the distressing thoughts and feelings that it evokes), ACT focuses on helping patients to cultivate acceptance and reduce the dominance of the distressing thoughts and beliefs on behavior, an empowering stance that prevents fatigue from becoming a barrier to moving towards the people and activities that are most important to them, such as spending time with loved ones (e.g., values-aligned behavior).[19]

Acceptance-based interventions such as ACT provide a strongly matched approach to patients with advanced cancer, who even under ideal care, will experience some degree of symptoms or side effects. In support, the one published randomized trial of ACT versus CBT for patients with late-stage ovarian cancer found that ACT led to superior outcomes, including for quality of life, anxiety, depression, distress, and acceptance, by large and significant effects.[20] This study was small, did not target fatigue, and required 12 face-to-face individual intervention sessions, which remains unscalable, but it nevertheless demonstrates the promise of ACT for the targeted population. Given the range of difficulties and high symptom burdens associated with advanced ovarian cancer,[12, 21, 22] novel approaches that leverage shared intervention principles to address multiple behavioral issues in a single intervention—including fatigue, distress, and fear of cancer recurrence—are urgently needed.

Few ACT-based intervention studies have investigated the changes in fatigue. Dr. Arch (co-PI) conducted a group-based ACT intervention for anxious cancer survivors and found significant improvements in cancer-specific distress and fatigue, as well as fear of cancer recurrence in a single-arm pilot trial.[23] She next conducted a randomized controlled trial of this ACT intervention versus enhanced usual care (EUC) for anxious cancer survivors. The final analyses, which are in preparation for publication, demonstrate that ACT led to superior reductions on all three of these outcomes (fatigue, cancer-specific distress, and fear of cancer recurrence) relative to EUC, through 6-month follow-up (the longest time point studied).[24] Further, compared to EUC, the ACT intervention led to fewer missed medical appointments. A

third study by Dr. Arch adapted ACT into a briefer format that alternated group and online sessions, and specifically targeted anxiety, depression, and advanced care planning engagement among anxious and depressed patients with stage IV cancer (mixed solid tumor types).[25] Though fatigue was not a targeted outcome, this briefer ACT intervention for patients with metastatic cancers showed promising pilot findings, including feasibility and acceptability, and significantly reduced anxiety, depression, and fear of dying, along with significantly increased rates of advanced care planning. This study also demonstrates Dr. Arch's ability to adapt ACT into scalable formats that meet the needs of patients with metastatic cancers. This study will build upon our earlier work to test a novel ACT intervention for women with advanced ovarian cancer who experience moderate-severe PARPi-related fatigue.

3.2 Rationale

REVITALIZE meets a critical unmet need for women with advanced ovarian cancer who experience fatigue on PARPi. The proposed ACT intervention represents an innovative and systematic attempt to address PARPi-related fatigue. Additionally, this study harnesses telehealth as a scalable strategy to improve symptom management and QOL. The intervention will use a HIPAA-compliant telehealth platform for intervention delivery (Zoom for Healthcare), enabling us to draw patients from broader geographic areas, including rural areas. Results from this research will inform the design and conduct of a multicenter RCT to test the effectiveness of REVITALIZE among patients with advanced ovarian cancer on PARPi. If successful, REVITALIZE will provide a scalable, patient-centered approach to improve symptom management and QOL for patients with advanced ovarian cancer on PARPI.

4.0 Inclusion and Exclusion Criteria

4.1 Inclusion criteria

- Women ≥18 years of age who have been diagnosed with epithelial ovarian, fallopian tube, or primary peritoneal carcinoma.
- Receiving PARPI inhibitors for ≥ 2 months.
- Able to read/speak English.
- Have an Eastern Oncology Group (ECOG) performance of 0-2.
- Report moderate-severe fatigue in the past week (average score ≥4 on a Fatigue Symptom Inventory scale of 0-10)

4.2 Exclusion Criteria

- Patients with an untreated clinical condition or comorbid illness (e.g. anemia, hypothyroidism) that could explain their fatigue.
- Patients with chronic severe fatigue that pre-dates their use of PARPi.

The following special populations will be excluded from this research:

- Adults unable to consent
- Individuals who are not yet adults (infants, children, teenagers)
- Pregnant women
- Prisoners

5.0 Study-Wide Number of Subjects

Before initiating the RCT, we will pre-pilot the REVITALIZE intervention in up to 5 patients at the Dana-Farber Cancer Institute (DFCI). This run-in phase serves to test and refine the newly developed 6-week ACT intervention in a smaller sample size prior to initiating the RCT portion of the study. After we've tested and refined the ACT intervention, we will enroll and randomize up to 50 fatigued patients with advanced ovarian cancer on maintenance PARPi at Dana-Farber Cancer Institute and the Abramson Cancer Center at the University of Pennsylvania, to ensure 40 evaluable participants. Participants will be randomized to receive either a 6-week ACT intervention or enhanced usual care (educational materials). 20-25 patients will be enrolled to each study arm.

6.0 Study-Wide Recruitment Methods

6.1 <u>Screening and Recruitment</u>

This is a two-arm, multi-center pilot randomized trial to compare the feasibility, acceptability, and preliminary efficacy of REVITALIZE, a 6-week ACT intervention vs. enhanced usual care in up to 50 fatigued patients with advanced ovarian cancer. We will enroll patients from the DFCI Gynecologic Oncology Program and the Abramson Cancer Center at University of Pennsylvania. Study staff, oncology providers and other members of the oncology team will identify patients who may be eligible for this study. Prior to obtaining informed consent, study staff will review electronic medical records of patients listed on the oncology providers' clinic schedules to identify patients with advanced ovarian cancer who are on PARPi. These patients' medical records will only be reviewed to confirm this protected health information (PHI), and it will only be shared in the context of patients' eligibility for the study.

When an eligible patient is identified, study staff will contact the patients' oncology provider to confirm they meet the eligibility criteria and to request permission to approach the patient at

either an upcoming clinic visit or remotely via telehealth procedures (over the phone or via Zoom). Participants who are recruited remotely will be provided with a recruitment letter outlining additional details about the study, such as the procedures and time commitment involved (Appendix A). If the oncology provider deems the patient ineligible or too distressed to participate in a research study at this time, the patient will not be approached for inclusion. If the patient is approved to approach for enrollment, the study staff will coordinate with the oncology provider to meet with the patient to discuss the study at the time of their next clinic visit or at a time that is convenient for the patient. During this visit (in-person or remote), patients will be screened for the presence of moderate-severe fatigue in the past week (average score ≥4 on a Fatigue Symptom Inventory scale of 0-10). We will only actively screen eligible patients once. If a patient is deemed ineligible due to a lack of fatigue, but the patient or oncologist indicates that they have more fatigue later during PARPi and want to participate, we will re-approach the patient. Additionally, if the study team approaches a patient and they want to participate, but mention that now is not a good time, we will confirm with this patient if it is okay for the study team to re-approach them at another time. If they agree to be re-approached, we will note this in a secure password-protected screening and enrollment log, and re-approach the patient at another date.

PHI will not be shared with anyone outside of the study team and patients' oncology providers. A partial HIPAA waiver requesting permission to review the PHI of these select patients prior to consent during screening and recruitment has been submitted to justify this process.

6.2 Informed Consent

If a patient agrees to learn more about the study, a member from the study team will describe the study, review the consent form with the patient, answer any questions they may have, and provide their contact information. Appendix B will be used by the study staff member for a verbal consent script (Appendix B1 for Dana-Faber or Appendix B3 for University of Pennsylvania). The staff member will encourage patients to take their time in deciding whether they want to participate in the study or not.

If a patient is interested in participating, the staff member will obtain their informed verbal consent, which will include explaining why this research is being conducted, information about study procedures, the risks and benefits of participation, and how long the patient will be involved in this research study. The staff member will reiterate that the data collected are not a part of the patient's standard of care treatment and will underscore the importance placed upon maintaining patient confidentiality and a patient's rights while they are involved in the study. This includes the right to withdraw participation at any time for any reason during the study because participation is completely voluntary. All participants will be given a copy of the verbal consent form (Appendix B2 for Dana-Faber participants or Appendix B4 for University of Pennsylvania participants).

Patients will also be consented for medical record review so that we can examine their treatments, side effects, hospitalizations, and outcomes over time. The verbal informed consent form will contain a section dedicated to explaining what constitutes PHI and how this information will be protected as confidential per HIPAA guidelines. The verbal consent form will also provide contact information for both the Principal Investigator (PI) as well as the Office for Protection of Research Subjects.

Remote consenting will be permitted if a patient is unable to be approached in-person at an upcoming clinic visit. With permission from the patient's oncology provider, study staff will send the potential patient a recruitment letter via mail or email to provide them with more information about the study, and to allow them to opt out of being contacted (Appendix A). Study staff will then follow up by phone with all potential patients who do not opt out of further contact and send verbal consent forms for patients to review if they are interested in participating in the study. Consent forms will be sent either by mail, email, or electronically through a secure and personalized link in REDCap, depending on participant preference. The verbal consent forms will be IRB approved. During the consent discussion, study staff will emphasize that the study is voluntary, patients may withdraw from the study at any time, and that withdrawal of consent will not affect their medical treatment in any way. Consent discussions can be completed via phone or Zoom.

All informed consent processes will adhere to the policies set forth by the Institutional Review Board. Patient verbal consent will be documented and tracked in a secure password-protected screening and enrollment log and in the patient registration form in REDCap. Only study staff will have access to the enrollment log and REDCap database.

If a patient is unsure if they would like to participate in the study, they will be offered the consent form to review and the contact information of study staff. If the patient does not contact the staff after a 3-4 days and further contact is appropriate, the staff member will contact the patient to follow up. If a patient is not interested, the staff member will thank them for considering, and reassure the patient that the process will have no impact on their care. No further interactions will occur with patients who either decline or prove to be ineligible for the study. If the patient decides to participate, a staff member will engage in the informed consent process with the patient.

6.3 Subject Registration and Randomization

After informed verbal consent is obtained, participants will be assigned a unique study ID and registered to the study in REDCap. Participants will be retrospectively registered in OnCore, the Clinical Trials Management System (CTMS) for Dana-Farber in a de-centralized fashion. Registration may occur up to 30 days after verbal consent is obtained per REGIST-101.

To complete registration for participants at UPenn, the following documents should be completed by site staff and emailed to the Dana-Farber study team at: wrightlab@dfci.harvard.edu.

- Informed Consent Documentation
- Completed External Site Subject Registration Form
- Completed Fatigue Symptom Inventory (FSI) Indicating moderate-severe fatigue (average score ≥4 on the FSI scale of 0-10)

Note: Study coordinators or research assistants at external sites (defined as outside of the DF/HCC) may complete the checklist. At minimum, subject initials must be included. The remaining fields are not required for minimal risk trials. The local study coordinator/research assistant may sign the checklist as Screening Staff. An Enrollment Monitor signature is not required and may be marked as not applicable.

To complete the registration process, the Dana-Farber study team will:

- Follow the DF/HCC Standard Operating Procedure for Human Subject Research Titled Subject Protocol Registration (SOP #: REGIST-101) and register the participant on the protocol
- Call or email the site staff at the participating site to provide the participant study number and to confirm registration.

NOTE: Registration can only be conducted during the business hours of 8:00 AM and 5:00 PM Eastern Standard Time Monday through Friday.

The Dana-Farber study team will register and randomize applicable patients, instead of ODQ, because randomization will occur after the patient has signed informed consent (to minimize multiple visits/contacts for this minimal risk protocol). Enrolled participants will be randomized to one of two arms: 1) enhanced usual care, 2) REVITALIZE, a 6-week ACT-based intervention using a 1:1 ratio with a computer-generated random allocation sequence between conditions and stratification by site, with the sequence concealed until the data are finalized.

7.0 Multi-Site Research

This is a multi-site study. The lead and coordinating center for this protocol is Dana-Farber Cancer Institute. The Funding Organization for this study is the National Comprehensive Cancer Network (NCCN) and the Research Funding Provider is AstraZeneca. The regulatory sponsor is Dr. Alexi A. Wright, MD, MPH. The proposed research will take place at Dana-Farber Cancer Institute (Overall PI Alexi Wright, MD, MPH) and the Abramson Cancer Center (Site PI Anna Smith, MD, MPH, MSc). MPI Dr. Joanna Arch, at University of Colorado, will

serve as the licensed psychologist supervising the study interventionists. The study interventionists will be clinical psychology doctoral students who have earned a master's degree in clinical psychology (hereafter referred to as "clinical psychology trainees"). The Data Safety Monitoring Plan for this project is located in Appendix C.

7.1 Regulatory Sponsor and Coordinating Center

The regulatory sponsor, Dr. Alexi Wright, MD, MPH, will accept responsibility for all aspects of conducting this multi-center protocol, which includes but is not limited to:

- Oversee the coordination, development, submission, and approval of the protocol as well as subsequent amendments.
- Ensure that investigators, study team members, and other research staff are qualified and appropriately resourced to conduct the protocol.
- Make sure that all sites are using the correct version of the protocol and that each participating site has adequate protocol training (and/or a Site Initiation Visit prior to enrolling participants) and throughout the trial's conduct as needed.
- Monitor progress and overall conduct of the study at all Participating Institutions.
- Ensure compliance with all requirements as set forth in the Code of Federal Regulations, HIPAA requirements, the approved protocol, and site-specific requirements.

The general responsibilities of the Coordinating Center may include but are not limited to:

- Review registration materials for eligibility and register participants from Participating Institutions in the DF/HCC clinical trial management system (CTMS).
- Distribute protocol and informed consent document updates to Participating Institutions as needed.
- Oversee the data collection process from Participating Institutions.
- Maintain Regulatory documents of all Participating Institutions which includes but is not limited to the following: local IRB approvals/notifications from all Participating Institutions, confirmation of Federalwide Assurances (FWAs) for all sites, all SAE submissions, Screening Logs for all sites, IRB approved consents for all sites
- Conduct regular communications with all Participating Institutions (conference calls, emails, etc.) and maintain documentation all relevant communications.

If the outside sites have any questions or concerns throughout the study, the study team and Overall PI will be available to assist.

8.0 Study Timelines

Each individual subject will remain in the study for the duration of the intervention and follow-up assessments, which is approximately 3 months once the intervention begins. Participants in the run-in phase will remain in the study for the duration of the intervention, approximately 6 weeks. We expect to be able to recruit our target sample size of up to 55 (run-in phase + pilot RCT) patients over the period of 18 months. The study team anticipates completing data analysis within 6 months of study completion.

9.0 Study Endpoints

9.1 Primary Endpoints

1) To assess the feasibility and acceptability of REVITALIZE, a pilot RCT designed to help women with advanced ovarian cancer manage PARPi-related fatigue and estimate outcome parameters for a full-scale RCT.
    a. Feasibility will be defined as ≥50% approach-to-enrollment rate of eligible participants and ≥70% completion of 3-month outcome assessments.
    b. Acceptability will be defined ≤20% withdrawing from the study overall, and ≤20% of participants on the intervention arm reporting high study burden.

2) To compare changes in fatigue (FSI) from baseline to 8- and 12-weeks.

9.2 Secondary Endpoints

1) To compare changes in emotional distress (GAD-7 and PHQ-8), fear of cancer recurrence (FCRI), and quality of life (FACT-O) at baseline, 8- and 12-weeks.

9.3 Exploratory Endpoints

1) To explore patient adherence to PARP inhibitors (Voils Measure).

2) Explore whether process outcomes (i.e., catastrophizing, fatigue self-efficacy, psychological flexibility, experiential avoidance, values) change from baseline to 4-, 8-, and 12-weeks.

3) Explore the trajectory of change in process and outcome measures from baseline to 4-, 8-, and 12 weeks to determine at what point in treatment changes start occurring.

10.0 Procedures Involved

10.1 Design/Study Type

First, we will test and refine the REVITALIZE intervention in a sample of up to 5 patients with ovarian cancer who report fatigue associated with PARPi in a single-arm pre-pilot run-in phase of a 6-week ACT intervention (REVITALIZE). We will then enroll up to 50 patients (to ensure 40 evaluable patients) with advanced ovarian cancer who report fatigue associated with PARPi treatment to a pilot RCT to assess the feasibility, acceptability, and preliminary efficacy of REVITALIZE vs. enhanced usual care (EUC). See Sections 10.31 and 10.34 for more information about each study arm.

We will recruit cohorts of patients at each site and randomize half of the sample to REVITALIZE and half to EUC. Participants randomized to REVITALIZE will receive 6 weekly sessions lasting approximately 60-75 minutes over a 6-8 week period, delivered face-to-face using iPads, computers or tablets, and a HIPAA-compliant platform (Zoom for Healthcare). If participants have difficulty connecting to the platform, telephone sessions are permitted. Participants randomized to EUC will receive educational materials developed by the National Comprehensive Cancer Network (NCCN) about fatigue and exercise during cancer treatment.

Based upon participant and interventionist feedback from the pre-pilot, we will allow participants up to 8 weeks from the start of the intervention for completion of the 6-week intervention and 60-75 minutes per session. During the pre-pilot 2/4 participants needed to reschedule 1 session, which made it challenging to deliver the intervention in 6 weeks. Similarly, 2/4 participants required more than 60 minutes per session, as each session ends with an experiential exercise and participants had varying responses to this (several experienced insights during this moment and wanted to debrief with the interventionist afterwards). To minimize study burden, if a session is running >60 minutes the interventionist will offer the participant a choice of whether to continue or table the remaining content to the next week, emphasizing that there is no expectation from the interventionist to continue. Additionally, we have added one “booster session,” which will take place 4 weeks after intervention completion. This session is designed to reinforce and enhance the skills acquired during intervention. No new skills will be included, but we will help participants troubleshoot areas needed to be worked on as participants integrate the skills that they learned during the intervention into their lives without interventionist support. Finally, it will also help hold study participants accountable for maintaining behavior change after intervention completion, helping to reinforce habit formation.

During the pre-pilot, we also recognized that we did not assess process measures (i.e. patient catastrophizing, fatigue self-efficacy, psychological flexibility, experiential avoidance,

values) until after intervention completion. In the revised protocol we will add another assessment at 4 weeks post-intervention start to enable us to explore whether these process measures change during the intervention. Additionally, to assess participant's satisfaction with each session we will ask the interventionists to perform a brief assessment of the "Session Rating Scale" after each session.

After all patients have completed the intervention, we will conduct a preliminary analysis to assess our aims of feasibility and acceptability. Feasibility will be defined as ≥50% approach-to-enrollment rate among eligible participants and ≥70% completion of 3-month outcome assessments. Acceptability will be defined ≤20% withdrawing from the study overall, and ≤20% of participants on the intervention arm reporting high study burden.

We will also examine the effects of REVITALIZE on fatigue (primary outcome); psychological distress, fear of cancer recurrence, and overall QOL (secondary outcomes); and adherence and process outcomes, including additional measures of acceptability at study-completion (exploratory outcomes).

Our final analyses will provide preliminary estimates of the feasibility, acceptability, scale scores, missing data, and participant feedback.

10.2 Selection of Instruments

The following validated measures will be used in the study surveys at baseline (*Participant Baseline Interview*, Appendix D), 4-, 8- and 12-weeks post-intervention start (*Participant Post-Baseline Interview* Appendix E) to assess primary outcomes (fatigue), secondary outcomes (emotional distress, fear of cancer recurrence, quality of life), exploratory outcomes (adherence), and process outcomes (catastrophizing, fatigue self-efficacy, psychological flexibility, experiential avoidance, values, and therapeutic process).

All participants will be compensated for their time and effort by receiving a $20 gift card for completing each survey plus a $5 bonus for completing their survey within 48 hours of our sending or administering it—up to $25/survey, $100 for all four.

10.21a Fatigue Symptom Inventory (FSI)

The Fatigue Symptom Inventory is a tool designed to assess the severity, frequency and daily pattern of fatigue, as well as its perceived interference with daily functioning.[26, 27] It is a 14-item, 11-point rating scale developed to assess subjective fatigue. Severity is measured on 11-point scales that assess most, least, and average fatigue in the past week as well as current fatigue. Higher scores indicate greater levels of fatigue. Frequency is measured as the number of days in the past week (0-7) that patients felt fatigued as well as the extent of each day on average they felt fatigued. Perceived interference is measured on separate 11-point scales from 0 (no interference) to 10 (extreme interference) that assess the degree to which fatigue in the past week was judged to interfere with general levels of activity, ability to bathe and dress, normal work activity, ability to concentrate, relations with others, enjoyment of life,

and mood. The interference items can be summed to obtain a total perceived interference score.

10.21b General Anxiety Disorder Questionnaire (GAD-7)

The Generalized Anxiety Disorder 7-Item (GAD-7) is a reliable and validated self-report measure to assess anxiety symptoms. Respondents rate how often they have been bothered by 7 anxiety symptoms over the past two weeks using the following scale: 0 = Not at all; 1 = Several Days; 2 = Over half the days; and 3 = Nearly every day. Respondents also answer a question to assess the duration of their anxiety symptoms. Responses are tallied, and the total score indicates the presence and severity of GAD.[28] The measure has been validated in the general population[29] and is the recommended evaluative measure for anxiety in adult patients with cancer in the 2014 American Society of Clinical Oncology (ASCO) Guideline Adaptation.[30]

10.21c Patient Health Questionnaire-8 (PHQ-8)

The Patient Health Questionnaire-8 is a validated self-report measure that assesses eight depressive symptoms (excluding self-harm) using the Diagnostic and Statistical Manual of Mental Disorders (DSM) diagnostic criteria for major depressive disorder.[31] It is used to screen, diagnose, and monitor depressive symptoms[32] and has demonstrated validity in cancer patients.[33, 34] Respondents report if each symptom has bothered them “not at all”, “several days,” “more than half the days,” or “nearly every day” during the previous two weeks to measure their mental and emotional health.[35]

10.21d Fear of Cancer Recurrence Inventory (FCRI)

To measure fear of cancer recurrence (FCR) we will use the 42-item Fear of Cancer Recurrence Inventory (FCRI). This survey has been validated across diverse cancer populations, has strong psychometric qualities, and is the most comprehensive multi-dimensional scale of FCR available.[36, 37] Items are scored on a Likert scale ranging from 0 (“not at all” or “never”) to 4 (“a great deal or “all the time”). Higher scores indicate higher FCR. The FCRI is both internally consistent (Cronbach’s α=0.75 to 0.91 across subscales) and stable over a two-week interval (ρ = 0.58 to 0.83 across subscales). It also has convergent validity with other standardized measures of FCR (ρ = 0.66 to 0.77) and discriminant validity with QOL amongst a large sample (n = 600) of Canadian cancer patients with varying tumor types.[36]

10.21e Functional Assessment of Cancer Therapy-Ovarian Cancer (FACT-O)

Participants’ quality of life (QOL) will be assessed with the Functional Assessment of Cancer Therapy-Ovarian Cancer, which has demonstrated internal consistency, reliability, and

validity.[38] This measure is composed of the Functional Assessment of Cancer Therapy-General scale, with an ovarian cancer-specific subscale (OCS) included. The measure is divided into five primary QOL domains: physical well-being (7-items), social/family well-being (7-items), emotional well-being (6-items), functional well-being (7-items), and additional concerns (OCS subscale, 12-items).[38] Participants will rate each symptom over the past 7 days as: 0) Not at all; 1) A little bit; 2) Somewhat, 3) Quite a bit, and 4) Very much. Subscales can be analyzed separately or aggregated to produce a total score.

10.21f Medication Adherence Measure (Voils Measure)

We will use a validated self-report measure to assess dual conceptualizations of patient medication nonadherence—the extent of patient nonadherence and reasons for nonadherence.[39] Comparison measures include medication self-efficacy, beliefs about medications, impression management, conscientiousness, habit strength, and an existing nonadherence measure. The extent of nonadherence is measured with three positively correlated items, and reasons for nonadherence are assessed using several independent items.[39] Unlike extent of nonadherence, reason items are treated individually and descriptively, while extent items are averaged into an overall score. The three extent items can be used to help identify nonadherent patients and reason items can be used to identify and tailor intervention targets.

10.21g Fatigue Catastrophizing Survey (FCS)

We will assess participant catastrophizing using the Fatigue Catastrophizing Survey (FCS). Catastrophizing is a psychological process that can negatively contribute to the intensity of symptoms patients may be experiencing and increase a patient's level of distress, thus impacting their quality of life.[40] Modified from the Catastrophizing Scale of the Cognitive Coping Strategies Inventory (CCSI), this survey measures 10 fatigue-related items that reflect patients' tendencies to engage in overly negative thoughts (i.e. "I worry all the time" or "I feel I can't go on"). Patients rate each question on a 5-point scale (1=never true to 5=all of the time) to indicate how often each item is true for them when they've experienced fatigue. In prior research, more catastrophizing (as indicated by higher scores on the FCS) were associated with more severe fatigue in women with breast cancer.[41]

10.21h Fatigue Self-Efficacy

Self-efficacy concerning fatigue (i.e. the belief in one's capabilities to execute behaviors) will be measured with the 7-item Self-Efficacy Scale (SES28).[42] Items are scored on a 4-point Likert scale, and total scores range from 4 to 28. Higher scores indicate a greater sense of control over fatigue.

10.21i Acceptance and Action Cancer Questionnaire (AAQ-cancer)

We will measure changes in psychological flexibility (ACT processes) using a 15-item measure adapted from the widely validated AAQ-II and diabetes-adapted AAQ towards cancer specific items.[23] Numerous adaptations of the AAQ towards specific clinical targets have been shown to produce valid measures that mediate ACT outcomes for the specific population.[23]

10.21j Brief Multidimensional Experiential Avoidance Questionnaire (BEAQ)

The Multidimensional Experiential Avoidance Questionnaire is a 62-item measure developed to assess six domains of experiential avoidance (EA).[43] These domains are behavioral avoidance, distress aversion, procrastination, distraction and suppression, repression and denial, and distress endurance. For this study, we will use the abbreviated version of this measure, the Brief Multidimensional Experiential Avoidance Questionnaire (BEAQ) which only includes 15-items and covers all dimensions of experiential avoidance. This measure is internally consistent and has been broadly associated with psychopathology and quality of life.[44]

10.21k Valuing Questionnaire (VQ)

A primary objective of ACT is to facilitate valued living. We will use the 10-item Valuing Questionnaire (VQ) to assess personal values enactment during the past two weeks.[45] Respondents rate on a 6 point scale (0 “not at all true” to 6 “completely true”) how often each item was true for them during the past two weeks and evaluate using a two-factor scale; the Progress scale and Obstruction scale.[45] High VQ Progress scores are associated with positive affect, satisfaction with life, purpose in life and mastery and self-acceptance, while high VQ Obstruction scores are associated with depressive symptoms and negative affect.

10.21l Session Rating Scale

After each REVITALIZE study session, interventionists will use the Session Rating Scale (SRS) to assess participant’s satisfaction with each session. The SRS is a brief 4-item measure developed by Miller, Duncan & Johnson (2002) that enables participants to rate each REVITALIZE study session based upon their therapeutic alliance with the interventionist, approach or method, goals and topics, and an overall rating. The SRS will be administered orally at the end of each session and a total score will be calculated based on responses. Total scores will be recorded in a graph for each session and scores < 35 will prompt a discussion with the patient about how to better meet their needs during the REVITALIZE intervention sessions. (See Appendix I).

10.21m Demographic Information

Basic demographic information will be collected for all participants including: age, marital status, race/ethnicity, education, household structure, income, and employment. The questions will only take a few minutes to complete. In addition, clinical information will be collected from patient's medical records including: stage, treatments (number of and specific treatments used), time since diagnosis of advanced ovarian cancer, ECOG performance status, genetic testing results, and the starting dose and date of PARPi treatment. We will also obtain the dates of prior dose delays and/or reductions and reasons for each.

10.21n Patient Interviews

We will also conduct qualitative interviews with patients in the intervention arm to further understand the challenges and facilitators of each intervention component. We will interview up to 20 patients, or until thematic saturation is met, sampling both from those who completed the study, and those who dropped out. With a focus on acceptability, relevance, and barriers to implementation, these semi-structured interviews will provide data on both intervention and context-level factors, enabling us to further refine the intervention and design a larger RCT. An interview guide is provided in Appendix F; in accordance with qualitative interviewing procedures, additional themes and topics that arise over the course of the study may be explored further in qualitative interviews, in addition to the list of questions in the interview guide.

Interviews will be recorded to ensure that the interviewer adequately captures all feedback from patients. The consent forms for the study include information that the debriefing interview will be recorded, and we will also verbally request permission from patients to record the interview before starting the interview. We will not administer a qualitative interview to any person who does not consent to being recorded during the debriefing interview. All recordings of study sessions will be stored in secure, restricted-access locations. Recordings will be tied to a study ID number, and the only documents linking the patient's study ID to identifiable information are in a restricted-access file stored securely on restricted-access folders. Recordings of interviews will be transcribed for analysis using a DFCI-approved, HIPAA-compliant transcription vendor or locally at Dana-Farber. All patient identifiable information will be removed when the recordings are transcribed. Recordings of debriefing interviews will be destroyed when analyses are complete.

10.21o Pandemic Stress Index

To understand the impact of the novel coronavirus (or COVID-19) pandemic on study participants, we will administer the Pandemic Stress Index. Developed by researchers at the University of Miami, the Pandemic Stress Index is a 3-item measure used to assess behavior changes and stress that individuals may have experienced or are experiencing during the COVID-19 pandemic. The first item "What are you doing/did

you do during COVID-19 (coronavirus)?" assesses behavior changes in response to COVID-19. This includes changes that may have taken place in response to public health messaging (e.g., physical distancing, isolation, quarantine), changes in the workplace (e.g., working remotely, job loss), and changes to protect one's own or others' health (e.g. caretaking). The second item asks individuals to rate the overall degree to which COVID-19 has impacted their daily life, "How much is/did COVID-19 (coronavirus) impact your day-to-day life?" rated on a 5-point scale. Finally, participants are asked to report the psychosocial impact of COVID-19, "Which of the following are you experiencing (or did you experience) during COVID-19 (coronavirus)?" with a checklist of items pertaining to emotional distress, substance use, sexual behavior, financial stress, stigma, and support.[46, 47]

10.21p Acceptability of Intervention Measure (AIM)

A primary objective of our study is to evaluate acceptability, which will be defined as ≤20% withdrawing from the study overall, and ≤20% of participants on the intervention arm reporting high study burden. To more fully understand patients' experiences on the REVITALIZE arm, we will also use the 3-item Acceptability of Intervention Measure (AIM) to assess acceptability.[48] Items are measured on a 5-point Likert scale. Total scores range from 4 to 20. Higher scores indicate greater acceptability of the intervention.

10.3 Description of Interventions

This is a 12-week pilot randomized control trial. Prior to the start of the RCT, we will enroll up to 5 patients at Dana-Farber in a single-arm intervention testing phase of REVITALIZE. Upon completion of the run-in phase, we will enroll participants onto the RCT portion of the study. Eligible participants will be randomized to one of two study arms:

1) Acceptance and Commitment Therapy Arm (REVITALIZE)
2) Enhanced Usual Care (Educational Materials)

See the protocol schema (Section 1.0) for more details.

10.31 Intervention Arm (REVITALIZE)

The REVITALIZE intervention was developed by the study investigators based on evidence-based protocols for Cognitive Behavior Therapy (CBT) in advanced cancer and Acceptance and Commitment Therapy (ACT) based protocols used in patients with cancer.

The REVITALIZE intervention is a skills-based psycho-educational intervention that will target all processes of the ACT model of behavior change, including present moment, self-as-context, cognitive defusion, acceptance, values, and committed action. The intervention will also emphasize developing mindfulness skills and engaging in actions aligned with personal values. Participants randomized to the intervention arm will receive six 60–75-minute weekly sessions over a 6-8 week period delivered face-to-face using iPads or personal computers/tablets and a HIPAA-compliant platform (Zoom for Healthcare) or telephone (per patient preference).

We will provide psychoeducation about PARPi-related fatigue, including information on precipitating and perpetuating factors. During the six intervention sessions, we will work to identify the negative impacts associated with the struggle to control unwanted thoughts, feelings, and physical symptoms or side effects linked with advanced ovarian cancer and PARPi treatment. Patients will learn about the importance of balancing acceptance and behavior change strategies. We will use values-clarification exercises to formulate goals in behavioral terms, such as resuming activities or leisure interests. In addition, mindfulness and acceptance strategies will be used to foster psychological flexibility when faced with cancer-related barriers. Finally, cognitive defusion techniques will be taught to reduce the behavioral impact of negative thoughts and feelings associated with advanced cancer and PARPi-related fatigue. Patients will gradually work toward realizing their treatment goals that they formulated earlier. Although each participant will learn the same skills, session content and home practice will be tailored to individual patients' cancer-and fatigue-related experiences and other challenges. Patients will be provided with study workbooks (Appendix K) and will review many of these concepts with the interventionists during sessions, aided by diagrams (Appendix J). If the patient requests, we will allow for sharing of the audio recordings from the sessions to aid in review of core concepts. However, sharing of the audio recording from each session is not required.

Table 1 below provides a more detailed session-by-session overview:

Based on patient and therapist feedback from the run-in phase (4 patients, 4 therapists) and from the empirical literature showing that *flexible* application of intervention manuals is more effective than rigid application, we have built in greater flexibility into each session, allowing, for example, therapists to select one of any three specified metaphors for illustrating cognitive defusion, rather than having to use all three with all patients, or allowing them to spend more versus less time debriefing on patient's behavioral goals, depending on a given patient's goals and her difficulty in reaching them.

Session 1 --- Introduction and Psychoeducation	In this first session, we will focus on building rapport and taking a brief (cancer-related) history. We will provide basic psychoeducation on cancer-related fatigue and link this to triggers for fatigue (i.e. reinforcing the knowledge that PARP inhibitors are considered ongoing cancer treatment)

	as well as psychosocial factors that may add to this fatigue. We will elicit participants' fears and worries about their cancer and cancer treatment which may contribute to their fatigue. Participants who identify sleep disturbance as a barrier will be asked to complete a sleep diary as part of their home practice.
Session 2 --- Choice Point, Values, and Goals	After a brief acceptance-based meditation, the therapist will debrief and evaluate the previous session, as well as any barriers or thoughts that they observed in between sessions. We will introduce the Acceptance and Commitment Therapy (ACT) model to patients using the "Choice Point 2.0". In this educational exercise patients will learn about Towards and Away Moves, who and what are most important (values), and what gets in the way of accomplishing values-based behavior (barriers). Participants will be asked to complete a Choice Point on cancer-related fatigue and think about things that get in the way of working towards ones' values. This session will also focus on formulating values-based behavioral goals to explore what patients would be doing if they were no longer moderate-severely fatigued. Participants will be asked to set a Fatigue Action Goal, a small and doable behavioral activation goal (in the domains of sleep, activity or social support) for the next week that will be a part of each week's session.
Session 3 --- Challenging Feelings and What We Can and Can't Control	After a brief acceptance-based meditation, the therapist will debrief and evaluate the previous session, as well as any barriers or thoughts that they observed in between sessions. What are barriers to going towards values-based behavior, and what thoughts keep "hooking" patients? We will then select a metaphor/exercise or two (from a list, with an ability to tailor to a given patient) to help patients experience the "Illusion of Emotional and Cognitive Control". We will link these exercises to thoughts and emotions participants have in relation to cancer and fatigue and present alternative strategies. We will focus on recognizing that the struggle against difficult thoughts and feelings around the fatigue and the cancer itself, not the thoughts or feelings themselves, is the problem. We will use the "Struggle Switch", "Finger Trap", or related metaphors to illustrate that we cannot control how we feel but we can control the extent to which we struggle. Depending on time, we will end the session with or assign for home practice a meditation exercise about noticing and accepting thoughts and feelings. Participants will be asked to notice internal barriers (responses to thoughts, feelings, sensations) that get in the way of values-based behavior in their everyday lives between sessions.
Session 4 --- Detach from Thoughts and Beliefs that Hook Us	After a brief acceptance-based meditation, the therapist will debrief and evaluate the previous session, as well as any barriers or thoughts that they observed in between sessions. The main topic for this session is Defusion. We will focus on what's hooking them, what's getting in the way, how is your mind talking you out of this, what's stopping them from acting on these values or achieving goals. Importantly, the therapist will normalize and validate difficult thoughts/beliefs related to fatigue and cancer, which facilitates both acceptance and defusion. The goal is for participants to become more willing to have their thoughts without being unduly influenced by them, and reduce the energy they put into getting rid of them. The therapist will briefly summarize the main content of fusion, identify the relationship between fusion and behavior (away moves), and offer the possibility of learning a new approach as an alternative to fusion. We will use a metaphor (such as "The Hands as Thoughts and Feelings

	Metaphor" or Changing Radio Stations") to help the patient experience fusion and defusion. The basic idea of this and other defusion skills is that they create more distance between the participant and their thoughts and help them recognize that they aren't necessarily a part of who they are. We will explain that there are several helpful defusion skills that illustrate how to accept your thoughts while not identifying them or taking them too seriously. We will present participants with a handout of 10 common defusion techniques, briefly discuss them, and will ask participants to pick one or two that resonate with them and ask them to practice these in between sessions. Depending on the timing, the session will end with the Leaves on a Stream eyes-closed exercise or the next session will begin with this exercise.
Session 5 --- Flexibly Attaining Values and Goals	After a brief acceptance-based meditation, the therapist will debrief and evaluate the previous session, as well as any barriers or thoughts that they observed in between sessions. This session will include a more in-depth discussion and exploration of participants' values and goals. Values are chosen life directions; what you want to stand for; desired personal qualities. Values are like an "inner compass": they give us guidance, help us find a direction, stay on track, and help us find our way again when we go off track. We will help the patients distinguish values from goals and as needed help them connect with and clarify their values so they can use them to guide ongoing behavior. We will then move into committed action, translating values into ongoing, evolving, effective, dynamic patterns of overt and covert behavior (towards moves). We will focus on three skills: problem solving, goal setting, and action planning. We will use the "Challenge Formula" to help participants see they have choices, despite the difficult situation they are in. We all have limited time on this planet and cancer peels away the pretense that we are going to live forever, it peels away the curtain that keeps us away from our own vulnerability. It is very painful and associated with losses AND it's also an opportunity to re-evaluate who and what are most important to patients and to direct their energy towards that. We will then segue to committed action, on living by our values and acting effectively to achieve values-congruent goals. For some participants, helping them get in touch with their values and asking about values-congruent goals will be enough to get them moving, and they may have done this work already. For others, there may be some barriers and we'll look at what these are and how to overcome them. We will also assess the goals in terms of whether they are: a live person's goals, it is a realistic goal, what the payoffs are, and what plan B is. Particularly around fatigue, what if they have limited energy, what if they get really sick? Participants will be invited to engage in formal SMART goal setting and action planning in between this session and the last one.
Session 6 --- Integration, Review, and Future Planning	After a brief acceptance-based meditation, the therapist will debrief and evaluate the previous session, as well as any barriers or thoughts that they observed in between sessions. During this final session, we will review the skills that participants learned and identify a plan moving forward to promote daily vitality and coping with fatigue through the skills that spoke most strongly for the individual participant. We will create a plan even if fatigue worsens and will review and draw upon the home practice that they engaged in between session 5 and 6.
Booster Session --- Reinforcing and	This booster session will be provided 4 weeks after Session 6. This session is designed to reinforce and enhance the skills acquired during the

Enhancing Acquired Skills	intervention, while holding participants accountable for maintaining the behavior changes initiated during the intervention. No new skills will be included, but we will help troubleshoot areas needed to be worked on.

10.32 Zoom for Healthcare

Zoom for Healthcare is a HIPAA compliant telehealth platform that creates real-time and easy to use video communication solutions for the health care industry and enables secure, virtual healthcare delivery. The platform allows physicians, patients, and specialists to connect remotely across hospitals, clinics, homes and geographically isolated areas to raise levels of patient care and improve the delivery of treatment.

Additionally, this technology is easily integrated into site workflows to allow interventionists and patients to connect at specific dates and times, allowing enhanced control around who has access to appointments and when they take place.

If technical problems occur with the telehealth technology during a patient's scheduled virtual visit—or the patient expresses a preference for a telephone-based approach--then the trained REVITALIZE interventionist may switch to calling the patient and conduct the session via telephone. The REVITALIZE interventionist should notify the research team to address the technical issue prior to the patient's next ACT session. The study team may also contact patients via email, phone, or in-person to assist with technology set-up and troubleshooting.

10.33 Interventionist Training and Supervision

Interventionists will be master's level clinical psychology trainees. Prior to intervention delivery, interventionists will participate in a 3-day training provided by two topical experts in the areas of cancer-related fatigue and ACT (Drs. Poort and Arch, respectively), as well as ovarian cancer (provided by Dr. Wright). The training will provide the background and rationale for each of the intervention sessions and will involve active, evidence-based training methods, including role-playing with expert and peer feedback to practice intervention components. In addition, weekly supervision will be provided by Dr. Arch throughout the study. Drs. Arch and Poort will also provide additional ongoing weekly remote supervision to the interventionists with help from Dr. Wright. We will monitor study and intervention fidelity by using content checklists and the DFCI study team will analyze a random sample of recorded sessions (~10%) for content and quality. The DFCI study team will also have bi-weekly check-ins with the study teams at UC Boulder and UPenn to provide additional study oversight.

10.34 Control Arm (Enhanced Usual Care)

The Enhanced Usual Care arm will receive quality educational materials developed by the NCCN (Appendix G) about fatigue and exercise during cancer treatment.

10.4 Data Collection

Table 2 specifies the instrument and intervention data collection timeline.

Table 2. Study Measures and Data Collection

		STUDY TIMEPOINT			
		Baseline Visit	4 weeks post-intervention start	8 weeks post-intervention start	12 weeks post-intervention start
INSTRUMENT	Participant Baseline Interview	✓			
	Participant Post-Baseline Interview		✓	✓	✓
	Provision of NCCN Education Materials (EUC Arm Only)	✓			
	Debriefing Interview (REVITALIZE Arm Only)				✓
	Chart Abstraction Data	→	→	→	→

Data obtained via interviews, surveys, and chart abstractions will be stored on the Partners REDCap server.

10.5 Description of Study Process

10.51 Instrument Administration

Participant Baseline Survey:

- Participants will complete the interview on the same day informed consent is obtained; if this is not possible, then the survey may be completed at a subsequent visit or remotely (i.e. over the phone, via mail or email).
- All data from the interview will be stored in REDCap; if paper copies are used, they will be stored in restricted access locations.
- Estimated time to completion: 40-45 minutes

Participant Post-Baseline Survey:

- Participants will complete a post-baseline survey at about 4-, 8-, and 12-weeks post-intervention start. Surveys should be completed as

close to the projected assessment date, ideally within +/- 14 days. The flexible administration window accounts for variations in participants' schedules. The study team will account for delays in scheduling time with an interventionist (REVITALIZE arm) and mail delivery (EUC arm) when considering participants "intervention start date".

- Participants may complete the survey remotely or in-person.

Chart Abstractions:

- Study staff will review patients' medical records to complete the chart abstractions form at the time of the participants' baseline and post-baseline visits.

10.6 Special Concerns

10.61 Surveys

Participants will be contacted in advance to complete their upcoming study survey. After three unreturned voicemails and three unreturned emails, they will not be contacted again for additional surveys.

10.62 Discontinuation of PARPi

If a participant discontinues PARPi treatment due to disease progression or drug tolerability, they will be given the option to either continue on the study intervention or to withdraw. Participants who are no longer taking PARPi will be considered non-evaluable and will be replaced with a new study participant. See section 13 for further guidance on replacements.

11.0 Data Management and Confidentiality

11.1 Statistical Analysis

Primary Endpoints

1) To assess the feasibility and acceptability of REVITALIZE in women with advanced ovarian cancer who experience PARPi-related fatigue.
2) To compare changes in fatigue (FSI) from baseline to 8-weeks and 12-weeks.

Secondary Endpoints

1) To compare changes in emotional distress (GAD-7 and PHQ-8), fear of cancer recurrence (FCRI), and quality of life (FACT-O) at baseline, 8-weeks, and 12-weeks.

Exploratory Endpoints

1) Assess patient-reported adherence to PARP inhibitors (Voils Measure).
2) Explore whether process outcomes (i.e. catastrophizing, fatigue self-efficacy, psychological flexibility, experiential avoidance, values) change from baseline to 4-, 8-, and 12-weeks.
3) Explore the trajectory of change in process and outcome measures from baseline to 4-, 8-, and 12-weeks to determine at what point in treatment changes start occurring.

11.2 Sample Size and Statistical Power or Precisions

We have selected a pilot trial sample of up to 50 participants to allow us to: a) ensure 40 evaluable participants; b) recruit cohorts of the size needed for a future fully powered trial, to assess feasibility of recruitment and randomization; c) to pilot-test the intervention with multiple patients per site, allowing us to examine feasibility and acceptability within each site to establish a foundation for a future multi-site trial; d) obtain estimates of means and variance for each condition (the use of n=20 per condition allows for some stability in effect size estimates); d) assess usual/non-study care in both conditions, to examine the potential for use to be higher in EUC than the REVITALIZE arm. We will not include data from the 5 participants enrolled onto the run-in phase since this group of patients will not undergo randomization.

11.3 Data Analysis Plan

11.3a Feasibility/Acceptability

Feasibility will be defined as ≥50% approach-to-enrollment rate of eligible participants and ≥70% completion of 3-month outcome assessments. Acceptability will be defined ≤20% withdrawing from the study overall, and ≤20% of participants on the intervention arm reporting high study burden. Descriptive statistics will be used to summarize participants' demographic and clinical characteristics and to evaluate whether the trial has met its stated feasibility and acceptability endpoints for the portion consented, acceptability, and assessments completed. We will use basic inferential statistics ($\chi 2$ for categorical, t-tests or ANOVAs for dimensional DVs) to assess for the presence of systematic difference in feasibility between conditions. This will include a)

drop out patterns and characteristics between study arms; b) baseline characteristics between those lost to follow-up vs. retained.

11.3b Primary/Secondary Outcomes

Guided by NIH and statisticians' recommendations for the conduct of pilot trials and clustered trials, we did not power this small pilot trial to determine efficacy but to assess the feasibility of a fully-powered future RCT. Thus, we will evaluate means, standard deviations, and data clustering at each time point by condition. We will evaluate the clustering by cohort and recruitment site with intraclass correlation statistics. Additionally, we will examine the degree of usual/non-study supportive care use using descriptive statistics and will test association with condition. To examine trajectories of change over time by condition, we will use mixed effects repeated measures analyses that account for nested data. We will examine cohort and site as sources of variability and consider them as fixed or random effects as appropriate.

11.3c Qualitative Analysis

Qualitative interviews provide a critical lens to understand participants' experiences and perceptions. Thus, the analytic approach will be oriented toward framework analysis, a multi-stage coding process that includes both a priori defined and emergent codes. Through comprehensive indexing, charting, and mapping we will examine and compare within and across interviews to characterize the nature of the participant experiences with REVITALIZE and develop strategies for improving relevance and acceptability.

11.4 Data Management and Confidentiality

The study will be run by Dana-Farber Cancer Institute as the coordinating center. We will use the Partners REDCap infrastructure to capture information about study participants. All participant survey data will be specifically entered and maintained securely on the REDCap database. Only study staff members who have completed required institutional and study-specific training will have access to study data. All original copies of data will be kept in restricted-access locations, locked in file cabinets in study staff offices. Computerized databases will be password protected. Data will be collected, coded, and managed by study staff only. Data and software will be backed up on a nightly basis as per institutional norm. All recordings of study interviews and intervention sessions will be stored in secure locations in restricted-access, locked filing cabinets and in password-protected folders on the Dana-Farber servers. Recordings will be tied only to a study ID number, and the only document linking the patient's study ID to identifiable information will be in a restricted-access, password-protected files.

The study protocol will strictly adhere to all HIPAA and Dana-Farber and participating site regulations. Confidentiality of subjects will be maintained. No data will be linked to a particular name or personal identifiers. Only de-identified datasets will be provided for analysis.

12.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

No adverse events are expected in this minimal risk study; however, some participants may be distressed when answering questions about their fatigue and other symptoms. Study staff will monitor for adverse events during ACT intervention sessions or when they are interviewing participant, and either the participant or the interventionist can decide to end the interview, if needed. Should participants become exceedingly upset, disoriented or fatigued or need to attend to matters of personal care during the interviews or study visits, study staff will ask the subject if they would like to take a break or reschedule the survey for another time.

13.0 Withdrawal and Replacement of Non-Evaluable Subjects

Subjects are notified during the informed consent process that they may contact the study team in writing to request withdrawal of their complete data from use. If a participant decides to withdraw from the study, research staff will assure them that this will have no impact on their clinical care or relationship with their clinical oncology team.

If a participant has disease progression while on study, the participant may choose to continue the intervention, but will be deemed non-evaluable given disease progression can be accompanied by significant fatigue.

If a participant discontinues PARPi treatment due to disease progression or another medical reason (e.g. renal failure, severe cytopenias, cardiac arrhythmia), the participant may choose to continue the intervention, but will be deemed non-evaluable.

Regardless of evaluable status, we will give all participants on both arms the opportunity to continue the study surveys.

Non-evaluable participants will be replaced.

14.0 Risks to Subjects

We anticipate that this study will entail minimal risk to subjects. Discussing lived experiences with advanced cancer with a therapist or answering surveys about the emotional impact of cancer can be upsetting to some. Subjects will be informed of this minimal risk during the consenting process.

Should participants become exceedingly upset, disoriented or fatigued or need to attend to matters of personal care during the surveys, study staff will ask the subject if they would like to

take a break or reschedule the survey for another time. In the event that participants experience distress while completing surveys, we will follow standard procedures used in our behavioral health intervention studies for counseling and referral. The PI will be notified immediately, and participants will be provided with the pager number for the study PI in the consent form.

15.0 Potential Benefits to Subjects

There is no direct benefit to subjects taking part in the research. Subjects may benefit from awareness of fatigue as an important symptom that can be associated with PARPi and the potential for ACT to reduce this symptom, as well as a potential benefit of knowing that they have contributed to the generation of research that may help future patients.

16.0 Resources Available

16.1 Qualifications of Study Staff

Alexi A. Wright, MD, MPH (along with her collaborators Hanneke Poort, PhD and Joanna Arch, PhD) is well poised to execute the proposed research focusing on fatigued advanced ovarian cancer patients on PARP inhibitors because of her training, expertise, and experiences as a clinician-researcher focused in this area of study. As a member of the Gynecologic Oncology Program at the Brigham and Women's Hospital and Dana-Farber, she has access to patients on PARPi for advanced ovarian cancer and expertise in managing PARPi- associated symptoms. Within the group there are 10 medical oncologists, 6 gynecologic oncology surgeons, 2 radiation oncologists, 5 nurse practitioners, 1 physician assistant, 7 program nurses, 4 study nurses, and 12 research coordinators. Each year, the group cares for approximately 3,600 patients with gynecologic cancers, totaling 11,000 or more patient visits. It is a programmatic priority to involve all patients in therapeutic or outcomes trials. Dr. Wright will have all of the resources available to her at DFCI for the duration of this award, including statistical, research, and nursing support in addition to grants support and the support of the collaborating institutions participating in this work (DFCI, UPenn, and University of Colorado).

Hanneke Poort, PhD is a psychologist specializing in psychosocial oncology and palliative care. She successfully conducted several studies on cancer-related fatigue, including a similar adaptation study of CBT for patients on tyrosine kinase inhibitors for chronic myeloid leukemia, and a randomized controlled trial on the efficacy of CBT for fatigue in advanced cancer. In addition, she is involved in an active protocol (17-680, PI: Joffe) that studies the incidence, course, and predictors of fatigue developing on palbociclib in patients with advanced HR+ HER2- breast cancer. Dr. Poort is a member of the Department of Psychosocial Oncology and Palliative Care at Dana-Farber. The department provides world-class clinical care, while also conducting innovative, leading-edge research to help better understand the experience of living with cancer and identify novel approaches to improve quality of life.

Joanna Arch, PhD is a clinical psychologist at the University of Colorado. Over the past 8 years, Dr. Arch has led/leads four grant-funded studies of ACT interventions for cancer survivors with local cancer care centers. Dr. Arch, an early stage investigator, has strong institutional support from the University of Colorado and her department. First, Dr. Arch has a tenure-track appointment that reserves 40% of the academic year and 100% of the summer months for research. Second, Dr. Arch was given generous startup and retention funds of which sufficient funds remain to cover unexpected expenses on the proposed project. Third, as described above, Dr. Arch has ample designated space in which to conduct research, including ample space for the proposed project. Fourth, Dr. Arch's department and the university voted unanimously to grant her tenure and to promote her to Associate Professor, reflecting strong positive feedback and support. Drs. Arch and Wright have been working together since 2017 and have a paper under review together on anxiety among cancer survivors.

17.0 Provisions to Protect the Privacy Interests of Subjects

Only study staff that have completed all required institutional and CITI training and are familiar with the protocol will contact patients for an informed consent. Subjects will be given the opportunity to ask questions during the informed consent process, as well as during study participation. The informed consent includes information about the minimal risk of being uncomfortable with certain interview questions regarding patients' lived experiences with advanced cancer. Only study staff that completed training can access Epic. Study staff may conduct a limited review of a patient's medical record in order to schedule the interview and extract demographic and clinical data for research purposes.

18.0 Compensation for Research-Related Injury

This study involves minimal risk to subjects. Therefore, no compensation is available to subjects in the event of research-related injury. This is explained clearly in the informed consent.

19.0 Economic Burden to Subjects

There are no costs associated with study participation. Participants will be compensated for their time and effort by receiving a $20 gift card for completing each survey plus a $5 bonus for completing it within 48 hours of our sending or administering it—up to $25/survey or $100 for all four.

Appendices

Appendix A: Recruitment Letter

Appendix B: Telephone Script and Verbal Consent Template

Appendix C: Data Safety Monitoring Plan

Appendix D: Registration Form and Baseline Interview

Appendix E: Post-Baseline Interview

Appendix F: Participant Interview Guide

Appendix G: NCCN Educational Materials

Appendix H: External Site Registration Form

Appendix I*:* Session Rating Scale

Appendix J: Interventionist Slide Decks

Appendix K: Participant Workbook

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