

Examples of Funded Grants in Healthcare Delivery Research

Overview

The National Cancer Institute (NCI) frequently receives requests for examples of funded grant applications. Several investigators and their organizations agreed to let the Healthcare Delivery Research Program (HDRP) post excerpts of their healthcare delivery research grant applications online.

About

We are grateful to the investigators and their institutions for allowing us to provide this important resource to the community. We only include a copy of the SF 424 R&R Face Page, Project Summary/Abstract (Description), Project Narrative, Specific Aims, and Research Strategy; we do not include other SF 424 (R&R) forms or requisite information found in the full grant application (e.g., performance sites, key personnel, biographical sketches). To maintain confidentiality, we have redacted some information from these documents (e.g., budgets, social security numbers, home addresses, introduction to revised application).

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SF 424 R&R Face Page

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Title: Using MOST to EMPOWER: Optimizing an Emotion Regulation Intervention to Enhance Well-being Among Young Adult Cancer Survivors

FOA: PAR18-869

FOA Title: Modular R01s in Cancer Control and Population Sciences (R01 Clinical Trial Optional)

Organization: WAKE FOREST UNIVERSITY HEALTH SCIENCES

Department: PHS-Social Sciences

Senior/Key Personnel: John Salsman

Organization: Wake Forest University Health Sciences

Role Category: PD/PI

Project Summary

Young adult cancer survivors (YAs) are an important underserved group at risk for significant psychological distress. There are approximately 70,000 new diagnoses of cancer annually in YAs (ages 18-39), and currently nearly 2 million people in the United States are living with or have survived being diagnosed with cancer as a YA. Five-year survival rates of YAs are high (>80%) and YAs have approximately 35 to 59 years of life expectancy remaining, underscoring the importance of post-treatment survivorship care. YAs face unique challenges given the physical, cognitive, and psychosocial developmental milestones disrupted as a result of cancer and are at greater risk of psychological distress compared to older adults (ages ≥ 40) with cancer. Accordingly, YAs can benefit from targeted, supportive care interventions to decrease distress and enhance well-being as they navigate post-treatment survivorship.

Few psychosocial interventions have been developed for YAs or leverage eHealth modalities to provide supportive care and none have included a focus on enhancing psychological well-being through positive emotions. eHealth interventions represent promising options for patient engagement, especially with “digital natives” such as YAs. Given the ubiquitous nature of smartphones among YAs and their preference for remotely delivered interventions, the paucity of eHealth interventions among YAs is a missed opportunity. Moreover, although the deleterious effects of psychological distress are well-known, less attention has been focused on the benefits of psychological well-being. Psychological well-being is associated with better health outcomes, unique from the influence of distress, and includes domains inherently valued by young patients.

Our team has developed a novel, multicomponent intervention to enhance psychological well-being that shows promise among patients with HIV, diabetes, and breast cancer. We have piloted the intervention for YAs in an eHealth delivery format (EMPOWER: Enhancing Management of Psychological Outcomes With Emotion Regulation) to demonstrate feasibility and acceptability. By leveraging an innovative methodological design, the Multiphase Optimization Strategy (MOST), the main objective of our proposed study is to optimize EMPOWER for YAs and prepare for a future randomized clinical trial (RCT). To accomplish this, we propose the following specific aims: (1) Using a MOST framework, examine which of five components contributes meaningfully to well-being among YA cancer survivors; and (2) Identify mediators and moderators of component efficacy for well-being outcomes.

Upon completion of the testing, we will have a fully optimized, eHealth intervention to enhance psychological well-being among YA cancer survivors. This optimized intervention will be primed for a large, multi-site RCT and, as a scalable intervention, it will be ideally-suited for YA survivors who would otherwise not have access to supportive care interventions to help manage post-treatment distress and enhance well-being.

Project Narrative

Young adult cancer survivors (YAs) experience many challenges that increase distress yet no supportive care interventions exist for remote delivery to reduce distress and enhance well-being. Our main goal is to build off a pilot study of a multi-component, web-based, well-being intervention for YAs by collecting new data using an efficient research design to identify which intervention components work best. These data will guide future testing off the most effective (“best”) components of the intervention among YAs treated in community settings.

Specific Aims

Young adult cancer survivors (YAs) are an important underserved group at risk for significant psychological distress. There are approximately 70,000 new diagnoses of cancer annually in YAs (ages 18-39),¹ and currently nearly 2 million people in the United States are living with or have survived being diagnosed with cancer as a YA. Five-year survival rates of YAs are high (>80%)² and YAs have approximately 35 to 59 years of life expectancy remaining,³ underscoring the importance of post-treatment survivorship care. YAs face unique challenges given the physical, cognitive, and psychosocial developmental milestones disrupted as a result of cancer^{5,6} and are at greater risk of psychological distress compared to older adults (ages ≥40) with cancer.⁷⁻¹² Accordingly, YAs can benefit from targeted, supportive care interventions to decrease distress and enhance well-being as they navigate post-treatment survivorship.

The NCI has called for supportive care interventions in YAs to address psychological deficits.¹³ Unfortunately, few psychosocial interventions have been developed for YAs,^{14,15} few leverage eHealth modalities to provide supportive care,^{16,17} and none have included a focus on enhancing psychological well-being through positive emotions. eHealth interventions represent promising options for patient engagement, especially with “digital natives” such as YAs. Given the ubiquitous nature of smartphones among YAs and their comfort level with and preference for remotely delivered interventions,¹⁸ the paucity of eHealth interventions among YAs is a missed opportunity. Moreover, although the deleterious effects of psychological distress are well-researched, comparatively less attention has been focused on the benefits of psychological well-being. Psychological well-being is significantly associated with better health outcomes (better physical health,¹⁹ lower risk of mortality in healthy and chronically ill samples²⁰⁻²⁴), unique from the influence of distress, and includes domains that are inherently valued by patients (better relationships, more creativity, and better work quality²⁵).

Our team has developed a novel, multicomponent intervention to enhance psychological well-being that shows promise among patients with HIV, diabetes, and metastatic breast cancer, and we have piloted the intervention for YAs in an eHealth delivery format (EMPOWER: Enhancing Management of Psychological Outcomes With Emotion Regulation). Preliminary data suggest EMPOWER is feasible and acceptable to YAs. The purpose of our project is to optimize EMPOWER for YAs by determining which components are effective in promoting well-being and identifying demographic or individual difference variables that moderate EMPOWER’s impact. In addition, informed by Fredrickson’s Broaden and Build Theory²⁶ and Revised Stress and Coping Theory²⁷, we will explore mechanisms through which EMPOWER may yield benefits for YAs. To address these questions, utilize resources efficiently and prepare for a future randomized clinical trial (RCT), we will use an innovative methodological framework, the Multiphase Optimization Strategy (MOST),²⁸ to refine our eHealth intervention. MOST designs consist of efficient experiments on distinct intervention components to determine which could be retained or removed. These data inform assembly of an optimal, multicomponent intervention to achieve desired outcomes with minimal resource consumption and participant burden.²⁹

Thus, using a MOST design, we will first optimize EMPOWER to reduce distress and enhance well-being among YAs. To accomplish this, we propose two **Specific Aims**:

- 1. Using a highly efficient MOST framework, optimize EMPOWER by identifying which of five components contribute meaningfully to well-being among post-treatment, YA cancer survivors.** The five components tested will be: (1) noticing and capitalizing on positive events, & gratitude, (2) mindfulness, (3) positive reappraisal, (4) goal setting & personal strengths, and (5) acts of kindness. Primary outcomes will be positive affect, life satisfaction, depression, and anxiety. Secondary outcomes will be physical functioning, fatigue, satisfaction with social roles and responsibilities, and health behaviors.
- 2. Identify mediators and moderators of intervention component efficacy for the primary well-being outcomes.** We hypothesize that coping self-efficacy and social support will be significant mediators and the effect of intervention components on primary outcomes will be moderated by age and gender.

Impact: Upon completion of the testing, we will have a fully optimized, eHealth intervention to enhance psychological well-being among YA cancer survivors. This optimized intervention will be primed for a large, multi-site RCT and, as a scalable intervention, it will be ideally-suited for YA survivors who would otherwise not have access to supportive care interventions to help manage post-treatment distress and enhance well-being.

1. Significance

Young Adults with cancer are an underserved group. Approximately 70,000 young adults (YAs) are diagnosed with cancer annually, and an estimated 2,000,000 survivors of cancer are YAs. YAs have a high rate of un-insured and under-insured individuals, limited access to care, poor continuity of care, delayed diagnosis of cancer, poor participation in clinical trials, and unique supportive care needs.^{30,31} In addition, a cancer diagnosis and treatment for YAs may be especially disruptive given unique emotional and social life changes that take place during young adulthood (e.g., developing a positive body image and sexual identity, dating and building social networks, making decisions about higher education, careers, and family).^{5,6,32} These challenges often continue into post-treatment survivorship. Although the >80% 5-year survival rate for all diseases combined in YAs is comparable to that of pediatric patients (<15 years of age)², cancer is 6 times more common in YAs than in pediatric patients.³³ Compared to older adults with cancer who have a shorter life expectancy and poorer prognosis, YA survivors have approximately 35 to 59 years of life expectancy remaining,^{3,34} underscoring the importance of post-treatment survivorship care to address their unique needs.

YAs have clinically significant levels of psychological distress. Age-related disparities are present in rates of psychological distress. The prevalence of clinically significant depression or anxiety is much higher in YAs compared to older adults.^{9,10,35-39} For older adults, cancer is a distressing event but a more normative experience in an aging population. In addition, older adults typically have greater experience coping with major life events and thus greater coping self-efficacy (i.e., confidence in one's ability to manage stressful situations). For YAs, a cancer diagnosis is routinely unexpected, considerably disruptive, and frequently socially-isolating; factors that contribute to higher rates of psychological distress. Compared to pediatric and older adults with cancer, YAs may often have less engaged parental or family support and their peer networks may be less well-developed. Although YAs need and desire social support, there may be fewer interpersonal resources to rely on given their developmental stage (e.g., achieving independence from family, navigating new social networks), thus exacerbating their distress. Moreover, YAs with cancer are managing a chronic illness during their prime income earning years. They may have inadequate insurance coverage, limited financial assets, and experience significant work interruption, leading to greater financial strain and contributing to elevated distress.^{11,12}

The National Cancer Institute has identified a clear need for supportive care interventions in YA oncology. Sparked by the NCI and Livestrong Young Adult Alliance progress review recommendations in 2006,^{30,40} research in YA oncology has grown significantly. The National Comprehensive Cancer Network established guidelines for YAs as well as clinical practice guidelines for their oncology providers.^{41,42} The NCI-supported National Clinical Trials Network (NCTN) has YA-specific committees to strengthen intergroup collaboration and foster YA-specific protocol development.⁴³ In addition, the Institute of Medicine held a workshop in 2013 to review and evaluate progress in YA oncology since the 2006 progress review group report.^{44,45} This was followed by an NCI State of the Science meeting to discuss current research and gaps in the evidence-base for YA oncology across epidemiology, basic biology, clinical trials, health services/medical care, and health-related quality of life/symptoms.¹³ **One of the conclusions from the health-related quality of life/symptoms working group was that, "Supportive-care intervention studies are needed to address physical, psychological, and social health deficits among YAs with cancer..."**¹³

Few evidence-based interventions exist to address psychological deficits among YA cancer survivors. Unfortunately, few psychosocial interventions exist that have been *developed for and validated among YA cancer survivors*. Those that have been empirically evaluated include a socio-educational intervention to increase knowledge, promote lifestyle changes, and improve communication for young breast cancer survivors⁴⁶ and a physical activity intervention to promote exercise among post-treatment YAs of mixed cancer types.¹⁷ Although there may be indirect benefits to well-being from these interventions, no interventions to date have been developed and tested to reduce distress and promote well-being among post-treatment YAs.

Multi-component interventions show promise for improving psychological well-being. An advantage of psychological well-being interventions over other psychological and behavior change interventions is that activities to increase psychological well-being are inherently rewarding for participants and are thus more likely to be taken up as a habit. Lyubomirsky et al.²⁵ note several characteristics of successful psychological well-being interventions. An important characteristic is a match of the person to the activity. It is likely that different

activities will work for different people, so having several options to choose from may increase the likelihood that the intervention, as a whole, will have an effect. Accordingly, Moskowitz has developed a multi-component intervention comprised of 8 skills (positive events, capitalizing, gratitude, mindfulness, positive reappraisal, personal strengths, achievable goals, and acts of kindness) administered over 5 weekly sessions to promote psychological well-being. Her multi-component intervention has been adapted and tested in a number of chronic health conditions with promising results for addressing *dual* components of psychological well-being (i.e., decreasing negative and increasing positive; See Table 1).

Table 1: Moskowitz' Multicomponent Interventions to Improve Psychological Well-being	Sample	Delivery Modality	Depression	Positive Affect
Intervention for those Recently Informed of their Seropositive Status (IRISS) ⁴⁷	HIV+	In-person	$d = -0.18$	$d = 0.30$
Developing Affective Health to Improve Adherence (DAHLIA) ⁴⁸	Type 2 Diabetes	Online	$d = -0.35$	$d = 0.08$
Life Enhancing Activities for Family caregivers (LEAF) ⁴⁹	Metastatic Breast Cancer	Videoconference	$d = -0.81$	$d = 0.41$
Lessons In Linking Affect and Coping (LILAC) ⁵⁰	Caregivers of Patients with Dementia	In-person or online	$d = -0.25$	$d = 0.58$

Psychological well-being is an important primary outcome and inherently patient-centered.

Psychological well-being, which encompasses constructs such as positive affect, meaning and purpose, and life satisfaction is not simply the opposite of negative constructs like depression, distress, and anxiety. Psychological well-being has been described as having hedonic and eudaimonic components.⁵¹ Hedonic aspects of well-being are often more experiential in nature and emphasize pleasure (e.g., positive affect), whereas eudaimonic aspects of well-being are more evaluative in nature and emphasize human flourishing (e.g., meaning, life satisfaction). Diener et al. have posited an overall construct of subjective well-being, with correlated but separable components of life satisfaction, high positive affect, and low negative affect.^{52,53} Negative affect is often characterized by depressed or anxious mood states, whereas positive affect has been characterized as “feelings that reflect a level of pleasurable engagement with the environment such as happiness, joy, excitement, enthusiasm, and contentment” and contains both activated, excited and non-activated, peaceful components.⁵⁴ Psychological well-being is an important, patient-centered endpoint and provides positive associations with better physical health. For purposes of this proposal, we use the term psychological well-being to encompass positive affect/emotions, life satisfaction, and emotional well-being (characterized by low depression and low anxiety).

Psychological well-being interventions have a strong theoretical foundation. The relationship between psychological well-being and health is well-documented,^{19,55-61} and in the past decade, convincing empirical evidence has emerged suggesting that psychological well-being may be an important target for stress-reduction interventions given its relationship with health. Most striking, psychological well-being is associated with lower risk of morbidity and mortality in a number of healthy and chronically ill samples, independent of the effects of negative affect.^{19-21,23} Theoretical mechanisms by which psychological well-being impacts health have been proposed. Fredrickson suggested that psychological well-being serves a “broaden-and-build” function in individuals.²⁶ That is, psychological well-being enhances one’s social cognitive and problem-solving capabilities, thereby enhancing intrapersonal and interpersonal resources. This strengthening of one’s ability to manage stress (e.g., coping self-efficacy) and one’s external resources (e.g., social support) also enhance one’s well-being. Similarly, Revised Stress & Coping Theory²⁷ emphasizes the restorative role of positive emotions and the beneficial aspects of coping processes such as those advanced in Moskowitz’ multi-component intervention (positive reappraisal, positive events, capitalizing, achievable goals, etc.). Pressman and Cohen suggested psychological well-being has both direct and stress-buffering effects on health outcomes.¹⁹ In a direct effect model, physiological states associated with psychological well-being (e.g., sympathetic/ parasympathetic and brain activation) are directly associated with health outcomes; in the stress-buffering model, psychological well-being moderates relationships between stress and poor health outcomes. Therefore, leveraging psychological well-being to help mitigate post-treatment distress among YAs may prove particularly beneficial.

Interventions in cancer patients and survivors yield benefits for psychological well-being. One important question is whether psychological well-being can be changed and whether such changes are more

than transient.⁶² Critics argue for a genetically determined psychological well-being set point^{63,64} and while life events and circumstances can influence well-being temporarily, individuals eventually return to their set point.⁶⁵ This is the “hedonic treadmill” argument⁶⁶ – that individuals will continually seek greater well-being but will fall back to their set point. However, there is good empirical and theoretical reason to believe that psychological well-being can be increased in a lasting way⁶² and can, in turn, foster better physical and mental health.^{19,25} For example, there are a growing number of published interventions for cancer patients and survivors that promote health through enhanced psychological well-being. In separate controlled trials of women with breast cancer, cognitive-behavioral stress management⁶⁷, cognitive-behavioral therapy plus hypnosis⁶⁸, supportive expressive group therapy⁶⁹, expressive writing⁷⁰, and yoga^{71,72} interventions each yielded improvements in psychological well-being. In a study of prostate cancer survivors, telephone-delivered personal counseling resulted in more increases in psychological well-being than an educational intervention, but only for men with more social support and higher education, cancer knowledge and prostate-specific functioning.⁷³ While not an exhaustive list, these studies underscore the efficacy of psychological well-being for minimizing the negative impact of cancer and enhancing positive adaptation among patients and survivors.

Identifying efficacious components of multi-component interventions. Of course, multi-component interventions can be beneficial for participants, but it can be a challenge to identify which activities (or components) account for the beneficial effect(s). The Multiphase Optimization Strategy (MOST) for testing and evaluating interventions draws upon engineering principles to emphasize efficiency and strategic use of resources. MOST has been used to develop, optimize and evaluate smoking cessation^{28,74,75}, physical activity⁷⁶, weight loss⁷⁷ and fear of recurrence interventions.⁷⁸ Traditional RCTs evaluate multi-component interventions as a package and if effective, post-hoc analyses isolate active ingredients. For the purposes of this project, a MOST design is superior to traditional RCT designs and allows us to evaluate individual intervention components.

Leveraging eHealth modalities is critical for interventions with YAs. eHealth can be defined as technology-enabled processes, systems, and applications that expedite accurate, real-time health information, feedback, and skills training with the goal of advancing patient centered care.⁷⁹ This includes information delivered over the internet on desktop computers, and mobile and tablet devices.⁸⁰ Specific examples may include online health forums,⁸¹ short message service texts with health appointment reminders,⁸² and smartphone apps to monitor one’s heart rate⁸³ or daily activities.⁸⁴ A primary goal of eHealth applications is to facilitate accurate, real-time health information and skills training to empower patients’ self-efficacy for managing their health, improve patient care, and allocate resources in a more efficient, accessible, and cost effective manner. eHealth is a modern update of tailored health communication⁸⁵⁻⁸⁷ characterized by health resources that are personalized and contextually relevant to a targeted population. eHealth provides a novel way to utilize new technologies to enable access to healthcare resources and an effective means of engaging YAs, who are digital natives. Among U.S. adults ages 18-29 and 30-49, 92% and 88% have smartphones⁸⁸ and 99% and 96% use the Internet,⁸⁹ respectively. eHealth communication can be a vital system upon which to deliver support to commonly disenfranchised groups, such as YAs with cancer. Moreover, given the competing demands of young adulthood, YAs have expressed a preference for remotely delivered interventions specifically targeted to them,¹⁸ and a MOST design is well suited for eHealth interventions given the ease of manipulating multiple intervention components with an e-platform.^{78,79}

Significance Summary: Post-treatment YAs are an underserved group of cancer survivors at risk for clinically significant levels of distress. Multi-component interventions to promote psychological well-being hold promise for reducing distress and enhancing well-being but have not been evaluated among post-treatment YAs. To address this gap and respond to the NCI’s call for supportive care interventions that address psychological deficits in YAs, we developed a web-based intervention to promote psychological well-being (EMPOWER: Enhancing Management of Psychological Outcomes With Emotion Regulation). eHealth interventions provide a modality ideally-suited to YAs’ needs and preferences and can be easily administered and evaluated using a resource-efficient MOST design. This will allow us to optimize intervention content to identify “what works” and “for whom” in preparation for a subsequent R01 submission that would serve as a confirmatory pilot RCT of EMPOWER.

Lastly, but worth noting, our emphasis on interventions to enhance psychological well-being is not intended to deny, minimize, or otherwise ignore the significant stress of being diagnosed with and treated for cancer as a

YA or the deleterious impact it has on patients' psychological and physical health. Nor is it advocating a superficial "don't worry, be happy" approach to dealing with their illness. Rather, we are suggesting that if we broaden our focus to include a wider range of coping strategies, including interventions to promote psychological well-being, we will better equip YAs to manage the deleterious effects of stress.⁴

2. Innovation

Our proposed project is innovative in several respects.

First, psychosocial interventions to promote psychological well-being are infrequently tested in cancer survivorship despite their potential beneficial effects. In a series of meta-analyses of interventions that impact well-being outcomes in cancer (R03-CA184560; PI: Salsman), 31 RCTs with positive affect outcomes were identified.⁹⁰ However, only 5 of those RCTs (16%) were specifically designed to target positive affect or psychological well-being as a primary outcome,^{68,91-94} of which only 1 RCT (3%) was focused on post-treatment survivorship.⁹³ Our dual approach will allow us to impact psychological well-being by reducing and shortening psychological distress as well as increasing and sustaining psychological well-being.

Second, our approach is a web-based, eHealth intervention (EMPOWER, described below) that is platform neutral, allowing it to be accessible via desktop PC, tablet PC, or smartphone (both iPhone and Android systems). As already noted, YAs are "digital natives" and leveraging their technological aptitude for multi-component, tailored intervention delivery allows us to match their needs and preferences to supportive care content. Moreover, since EMPOWER is scalable, it can be simultaneously delivered to a limitless number of YAs at multiple and geographically diverse sites. Treatment integrity and fidelity to EMPOWER remain fully intact, reducing threats to internal validity. Thus, there is great long-term potential to reach YAs who are underserved and might not typically have access to psychosocial services through community-based practices where a majority receive care.^{30,95}

Third, we will employ the Multiphase Optimization Strategy (MOST) for testing and evaluating our EMPOWER intervention. The MOST framework is, in itself, innovative and particularly useful for building, optimizing, and evaluating multicomponent behavioral interventions. Having already built our individual intervention components, we will evaluate and optimize our EMPOWER intervention by assembling only those components with demonstrated efficacy. The optimized EMPOWER intervention will then be ready for confirmatory testing through a future randomized clinical trial (RCT).⁵¹⁻⁵³

Fourth, our proposal utilizes the state of the art in measurement of patient-reported outcomes by including emotional, physical, and social health measures from the NIH Toolbox⁹⁶⁻⁹⁸ and NIH Patient-Reported Outcomes Measurement Information System (PROMIS).⁹⁹⁻¹⁰¹ These psychometrically robust measurement systems have been systematically created through rigorous qualitative and quantitative measurement science methodologies, yielding measures that are reliable, valid, and responsive. Moreover, the ability to administer these measures as computer adaptive tests (CATs) minimizes respondent burden without sacrificing measurement precision. Thus, we can assess more content-relevant domains with fewer questions.

3. Approach

3.1. Research Team

Our strong research team has the necessary expertise and experience to successfully complete this project. Dr. Salsman (M-PI) is a clinical psychologist and leader in the field of adolescent and young adult oncology. He is the Co-Leader of the Cancer Prevention and Control Program and the Director of Clinical Research in Adolescent and Young Adult Oncology at the Wake Forest Baptist Comprehensive Cancer Center (WFBCCC). He will contribute to intervention refinement, recruitment and survey methodology specific to YAs, and patient-reported outcome measurement, including expertise in cutting-edge measures of psychological well-being.⁹⁷ He has an ongoing and productive collaboration with Dr. Moskowitz (M-PI), a social psychologist and internationally-renowned expert on the impact of positive emotion in adjustment to health-related stress. As previously described, she has conducted NIH and foundation funded interventions aimed at improving health

and health behaviors in a variety of acute and chronic health conditions. Together, they have collaborated on a meta-analysis of psychosocial interventions that impact positive outcomes (R03CA184560)⁹⁰ as well as an adaptation of a well-being intervention for metastatic breast cancer (LILAC)⁵⁰, for caregivers of dementia patients (LEAF)⁴⁹, and for young adult cancer survivors (EMPOWER; K07CA158008).^{102,103} They will be joined by Dr. Lynne Wagner (Co-I), a clinical psychologist and the Co-Director of the Cancer Control and Outcomes Program for the Eastern Cooperative Oncology Group-American College of Radiology Imaging Network (ECOG-ACRIN) Cancer Research Group. In addition to Dr. Wagner's wealth of experience conducting clinical trials through the National Clinical Trials Network, she has successfully conducted a MOST trial with a multi-component psychosocial intervention to reduce fear of recurrence in breast cancer survivors (FoRtitude; R21CA173193).⁷⁸ She and Dr. Salsman (Chair of the Adolescent and Young Adult Oncology Committee for ECOG-ACRIN) have worked together closely in their leadership roles within ECOG-ACRIN. This outstanding group of researchers also includes Co-Is with expertise in psychosocial oncology and cancer survivorship (Dr. Sanford), medical oncology with a particular focus on hematologic malignancies common in YAs (Dr. Howard), and quantitative methodology, including analytic approaches for MOST designs (Dr. Tooze). The group is further complemented by YA content expert consultants in psychological distress and survivorship (Dr. Zebrack), resilience and well-being (Dr. Rosenberg), and eHealth/mHealth interventions (Dr. Valle). All members of the research team have established collaborative relationships on a variety of projects related to YA oncology. The overall quality, intellectual depth, and multidisciplinary breadth of the investigative team should enable successful completion of the proposed work.

3.2. Preliminary Studies

We successfully adapted and tested a multi-component psychological well-being intervention for patients with metastatic breast cancer. Building off Dr. Moskowitz's past work developing interventions to promote psychological well-being among patients coping with health-related stress, we conducted a pilot RCT to examine the feasibility, acceptability, and preliminary efficacy of a five week psychological well-being intervention (LILAC: lessons in linking affect and coping) for women with metastatic breast cancer. This represented our first test of the psychological well-being intervention in a cancer sample.⁵⁰ Participants (N = 39) were randomized to an in-person intervention, online intervention, or in-person attention-matched control. Psychological well-being (depression, positive and negative affect) was assessed at baseline, 1 week post-intervention, and 1 month post-intervention follow-up. Our results showed that the LILAC intervention had good feasibility, retention, and acceptability: 49 of 100 screened patients expressed interest (49%) of which 39 (80%) were eligible, consented, and randomized; 79% of the sample was retained through the 1-month follow-up; adherence with the home practice was high (M=5.28 days/week), participants reported continued practice of the skills 1 month after intervention completion and indicated strong agreement they would recommend the intervention to their friends and to people diagnosed with breast cancer. The study was not adequately powered to detect between-group differences in change on preliminary efficacy outcomes, but within-group comparisons revealed that LILAC participants (in-person and online combined) showed reductions in depression and negative affect by the 1 month follow-up ($d = -0.81$). Notably, LILAC participants fell below the clinical threshold for depression (Center for Epidemiologic Studies Depression Scale = 16) by the 1 month follow-up ($t[17] = -2.22, P = .04, d = -0.52$), whereas control participants did not differ from threshold ($t[9] = 0.45, P = .66, d = 0.14$). *Online delivery of the intervention led to equivalent trajectories of change on preliminary efficacy outcomes as in-person delivery, and no differences were found between online vs. in-person conditions for acceptability ratings.*

Next, we reviewed and adapted intervention content for YAs as the initial step of our EMPOWER (Enhancing Management of Psychological Outcomes With Emotion Regulation) for post-treatment survivors. This iterative process included study team and stakeholder (YA survivors, psychosocial providers, medical oncology) review and input to determine skill and content language applicability for YA cancer survivors. Skills that were too narrowly focused were removed and the optimal sequence of skills was discussed. Content language was changed to reflect cancer survivorship experiences. For example, content language for the skill of positive reappraisal was changed to reflect commonly experienced feelings and cognitions of post-treatment survivors. All reviewers provided overall comments as well as specific feedback on the quality of the advice conveyed in each page, the affective response to the content, and the appropriateness of the supporting images. As a result of this feedback, minor modifications were made to content language (e.g., adding "fear" as a commonly experienced unpleasant emotion among cancer survivors) and images

(e.g., substituting an image in the Strengths lesson for one that is more broadly applicable to survivors who may have physical limitations).

Upon completion of this iterative review process, we had an EMPOWER intervention consisting of five sessions in which participants would learn behavioral and cognitive “skills” for increasing psychological well-being. The evidence-based components we identified for EMPOWER (Table 2) are consistent with Dr. Moskowitz’s multi-component well-being interventions, are drawn from positive psychotherapy¹⁰⁴ and originally developed as treatments for depression, but also have benefits for other aspects of psychological well-being. Positive Events, Capitalizing, and Gratitude (Week 1). Positive life events are associated with increases in psychological well-being^{105,106} and scheduling “pleasant events” is a component of some therapeutic approaches to treating depression.^{107,108} Further, by telling others about positive events, marking the

occurrences in some way, or even thinking about the events again later on, the association between positive events and psychological well-being is strengthened.¹⁰⁹ By capitalizing on or savoring the experience, it is possible to experience more psychological well-being without needing to find or create additional positive events. Similarly, feeling gratitude, thankfulness, or appreciation toward others, can further increase well-being.¹¹⁰⁻¹¹²

Mindfulness (Week 2). Mindfulness is defined as the ability to intentionally pay attention to and maintain non-judgmental awareness of one’s experience

(thoughts, feelings, physical sensations) in the present moment.¹¹³ Trait and state mindfulness are associated with higher psychological well-being and lower psychological distress.¹¹⁴ Interventions to increase mindfulness have been shown to increase positive emotion.^{115,116}

Positive Reappraisal (Week 3). The degree to which an event is experienced as stressful depends on the individual’s appraisal of the event and their resources for responding.¹¹⁷ Positive reappraisal is a form of coping in which the significance of the event is reinterpreted, or framed, in a more positive way and is one of the few ways of coping that is consistently associated with increased psychological well-being.^{118,119} Participants may seek out potential positive aspects of a situation without denying the situation, on balance, may be undesirable.

Focusing on Personal Strengths and Achievable Goals (Week 4). Social psychological research demonstrates that self-enhancing cognitions (thoughts about one’s positive qualities) are associated with better psychological adjustment to illness¹²⁰ and healthier biological profiles.¹²¹ Similarly, observational research on goals indicates that perceptions of goal progress are associated with greater life satisfaction and higher positive emotion.^{122,123} Pursuit of attainable goals (vs. more global distant goals) is associated with higher psychological well-being.¹²⁴

Altruistic Behaviors/Acts of Kindness (Week 5). Volunteerism and other altruistic behaviors are associated with lower risk of mortality^{125,126} and lower risk of serious illness¹²⁷ in large representative samples. Altruistic behavior may be associated with psychological well-being because it distracts one from his/her own problems, increases self-esteem, or increases a sense of mastery or general self-efficacy.¹²⁸

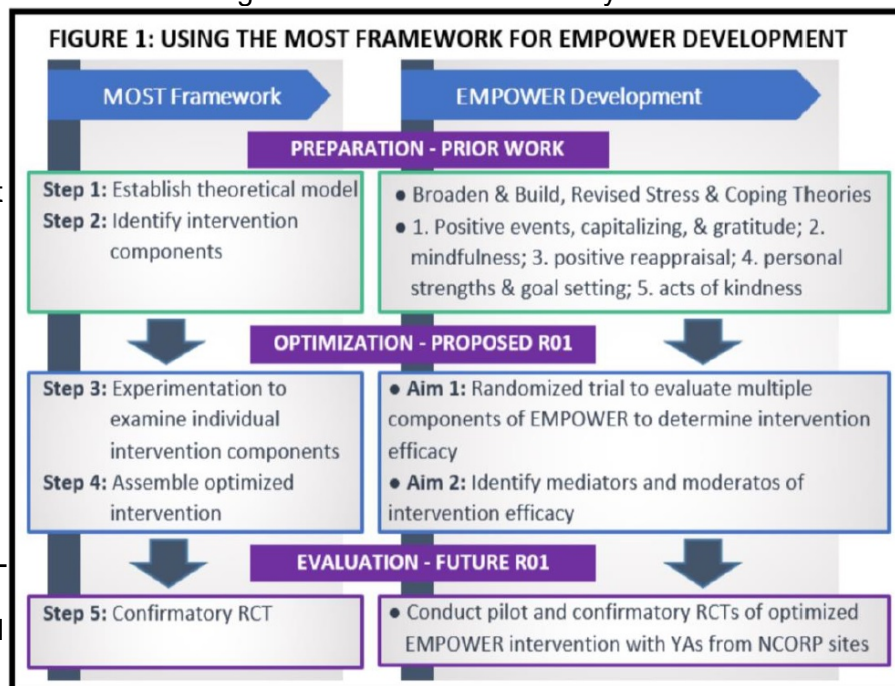
Session	Skills	Session Content
Week 1	1. Positive events 2. Capitalizing 3. Gratitude	1. Learning to recognize positive events (e.g., a good conversation with a friend, a good cup of coffee) and the associated positive affect. 2. Practicing ways to amplify the experience of positive events (e.g., taking an extra moment to savor the experience as it is happening, reliving the positive experience, telling someone else about the positive experience) 3. Taking a moment to feel thankful or appreciative of the things you have in life (e.g., family, a sunny day, a good night's rest)
Week 2	4. Mindfulness	4. Learn and practice the awareness and non-judgment components of mindfulness
Week 3	5. Positive Reappraisal	5. Understanding positive reappraisal and the idea that different forms of positive reappraisal can all lead to increased positive affect in the face of stress (e.g., seeing the "silver lining", finding out things weren't as bad as they could have been, seeing things weren't as bad as you initially thought they were, identifying good things that came out of the event)
Week 4	6. Personal Strengths 7. Achievable Goals	6. Participant lists his or her personal strengths and notes how they may have used these strengths recently (e.g., having a good sense of humor, being artistic) 7. Understanding characteristics of attainable goals and setting some goals for the week.
Week 5.	8. Acts of Kindness	8. Understanding that small acts of kindness can have a big impact on positive emotion (e.g., buying the person behind you in line a cup of coffee)

We pilot tested our EMPOWER intervention in two waves of a single arm study to evaluate feasibility and acceptability.^{102,103} A secondary aim was to evaluate preliminary data on psychological well-being (depression, positive affect, life satisfaction). Feasibility and acceptability were evaluated by recruitment and retention rates. Depression, positive affect, and life satisfaction were assessed at T1 (pre-intervention), T2

(post-intervention), and T3 (one-month follow-up). **The first wave of data collection occurred at the Robert H. Lurie Comprehensive Cancer Center of Northwestern (RHLCCC).**¹⁰² Through electronic medical record review over a six month period, we identified 185 potentially eligible YAs. *Eighteen YAs (10%, 16 women, M age=33.5) were eligible and consented. Thirteen participants completed all lessons (72% adherence) and assessments (72% retention) and indicated strong agreement they would recommend the intervention to their friends (M rating = 9 out of 10) or to a YA newly diagnosed with cancer (M rating = 8 out of 10).* Recruitment feasibility was suboptimal for EMPOWER but consistent with published rates. YAs have some of the lowest accrual rates to clinical trials with 6-14% participation in therapeutic trials and 8-20% in supportive care trials.^{129,130} Further, participation is poorer for YAs treated in adult settings (4-11%) compared to pediatric settings (26%-42%).^{131,132} Limited resources prevented us from following up with all 185 participants who were potentially eligible (all potentially eligible participants received a recruitment letter and 2/3 of the sample received a follow-up phone call). Thus, we believe our accrual rate is likely a conservative estimate and within the context of the published literature on YAs poor participation in clinical trials, our modest 10% rate is not unusual. Importantly, our acceptability ratings for the intervention were good. A majority of YAs appeared to enjoy the lessons as evidenced by their post-intervention ratings and our retention and adherence rates were good. In terms of secondary outcomes, A repeated measures ANOVA of psychological well-being scores revealed non-significant decreases in depression (Cohen's $d=0.30$) and non-significant increases in positive affect (Cohen's $d=0.18$) and life satisfaction (Cohen's $d=0.55$) from baseline to one-month follow-up ($P_s>.05$). YAs who dropped out reported more baseline depression ($P=.07$) and less positive affect ($P=.03$) and life satisfaction ($P=.001$). Although scores suggested modest benefits that generally remained at follow-up, our pilot study was not powered to detect intervention efficacy.

We recruited additional participants from the Wake Forest Baptist Comprehensive Cancer Center (WFBCCC), surrounding region, and online support communities for the second wave of data collection.¹⁰³ *We contacted 99 YAs and consented 23 (23.2% accrual; 16 women, M age=28.6). Retention (66.7%) and adherence (58.3%) rates decreased but data collection is ongoing (11 YAs still "on study"). Wave 2 participants also indicated strong agreement they would recommend the intervention to their friends (M rating = 8.5 out of 10) and to other YAs with cancer (M rating = 9 out of 10).* Based on feedback from Wave 1 "exit interviews" we modified the language of this last item from "To what extent would you recommend this intervention to someone newly diagnosed with cancer?" (Wave 1 wording) to "To what extent would you recommend this intervention to someone with cancer?" (Wave 2 wording) For Wave 2 secondary outcomes, psychological well-being scores revealed moderate but non-significant changes from baseline to 1-month follow-up for positive affect (Cohen's $d=0.41$) and depression ($d=-0.38$), but significant positive changes from baseline to for life satisfaction ($d=0.71$; $P=.006$).

Collectively, our data suggest that the well-being intervention can be feasibly disseminated as an online, web-based tool and is acceptable for patients with advanced breast cancer (LILAC) and post-treatment YAs (EMPOWER). Recruitment rates were low but consistent with published rates of clinical trial participation by YAs. Importantly, we were able to improve recruitment through a multi-modal approach (recruitment letters/emails/phone calls, messaging through patient portals, provider referrals, in-clinic recruitment) supplemented by community-based recruitment. This focused approach, supported by dedicated project



manager time and WFBCCC clinical trials recruiters, yielded positive gains in our accrual numbers for Wave 2. Although our pilot studies were not adequately powered to detect intervention efficacy, the magnitude of the effect sizes for depression were the largest of our well-being outcomes (Cohen's $d=.30$ to $.81$) with comparable effects for life satisfaction ($d=.55$ to $.71$). Optimizing the EMPOWER intervention will allow us to isolate and deliver only those components that are effective for post-treatment YAs. A fully-powered study is an essential next step to better understand which intervention components are efficacious and for which group of YAs.

3.3. Overview of the MOST Framework for Evaluating EMPOWER

The MOST design is comprised of three phases: preparation, optimization, and evaluation. Each of these phases corresponds to our past research, current plans, and future goals, respectively (See Figure 1). In preparation for this current submission, we devoted considerable thought to the theoretical underpinnings and specific components of the well-being intervention. The Broaden and Build²⁶ and Revised Stress and Coping Theories¹¹⁸ served as the basis for the well-being intervention (Step 1) which, combined with initial pilot testing, informed our five intervention components (Step 2). This current proposal is focused primarily on the Optimization phase of MOST. Aims 1 & 2 will be achieved through testing the individual intervention components of EMPOWER (Step 3). These data will then inform the creation of the optimized intervention (Step 4) that will be based on efficacy of the individual intervention components. This will lay the groundwork for the Evaluation phase of EMPOWER in a subsequent R01 (Step 5). For the Evaluation phase of MOST, we will pilot the optimized EMPOWER intervention using a sample of YAs recruited from community-based practices through NCORP and then conduct a larger, full-scale RCT which will examine the clinical and cost effectiveness of the intervention.

3.4. AIM 1: Using a highly efficient MOST framework, optimize EMPOWER by identifying which of five components contribute meaningfully to well-being among post-treatment, YA cancer survivors.

Guided by MOST, we will assign two levels (yes, no) to each of the five intervention components (2⁵). This will allow us to evaluate individual and combined intervention components in a classic full factorial design with 32 (2x2x2x2x2) experimental conditions (Table 3). Based on experimental condition, YAs will receive 0, 1, 2, 3, 4, or 5 EMPOWER components. A total of 352 participants will be randomly assigned to one of the 32 experimental conditions, resulting in 11 participants per condition. It is important to note that the factorial design in Table 3 should not be considered a 32-arm trial in which each condition is compared to a control condition. Our focus is on tests of standard ANOVA main effects and interaction effects. These tests involve comparison of means

Conditions	Component 1 positive events capitalizing gratitude	Component 2 mindfulness	Component 3 positive reappraisal	Component 4 personal strengths goal setting	Component 5 acts of kindness
1	N	N	N	N	N
2	N	N	N	N	Y
3	N	N	N	Y	N
4	N	N	N	Y	Y
5	N	N	Y	N	N
6	N	N	Y	N	Y
7	N	N	Y	Y	N
8	N	N	Y	Y	Y
9	N	Y	N	N	N
10	N	Y	N	N	Y
11	N	Y	N	Y	N
12	N	Y	N	Y	Y
13	N	Y	Y	N	N
14	N	Y	Y	N	Y
15	N	Y	Y	Y	N
16	N	Y	Y	Y	Y
17	Y	N	N	N	N
18	Y	N	N	N	Y
19	Y	N	N	Y	N
20	Y	N	N	Y	Y
21	Y	N	Y	N	N
22	Y	N	Y	N	Y
23	Y	N	Y	Y	N
24	Y	N	Y	Y	Y
25	Y	Y	N	N	N
26	Y	Y	N	N	Y
27	Y	Y	N	Y	N
28	Y	Y	N	Y	Y
29	Y	Y	Y	N	N
30	Y	Y	Y	N	Y
31	Y	Y	Y	Y	N
32	Y	Y	Y	Y	Y

computed across combinations of experimental conditions. This is a resource-efficient strategy that “recycles” participants in calculating main and interaction effects. Thus, the number of intervention components does not impact the sample size required.^{52,53} The main effect of each intervention component will be evaluated by comparing outcomes for participants who received the component (n = 176) versus those who did not (n = 176). For example, the main effect of the mindfulness component will be tested by comparing the mean of the outcome variable for the 176 subjects who receive mindfulness (i.e., those in Conditions 9-16 and 25-32 in Table 3) versus the mean of the outcome variable for the 176 subjects who do not receive mindfulness (i.e., those in Conditions 1-8 and 17-24). Similarly, the main effect of positive reappraisal will be tested by comparing the mean of the outcome variable for the 176 subjects who receive positive reappraisal (i.e., Conditions 5-8, 13-16, 21-24, and 29-32) versus the mean of the outcome variable for the 176 subjects who do not receive positive reappraisal (i.e., Conditions 1-4, 9-12, 17-20, and 25-28). Arms are balanced with regard to other intervention components, allowing a comparison of main and interaction effects. Therefore comparisons are based on 176 per condition, not 11. See “Sample Size” in 3.4.C. Analysis (below) for power calculations.

3.4.A. Participants

Eligibility. All YAs will meet the following inclusion criteria: (1) able to read and understand English, (2) past history of a cancer diagnosis (excluding basal cell skin carcinoma), (3) 15 to 39 years of age at diagnosis and currently between the ages of 18-39, (4) within 0-5 years post-active treatment (current hormonal treatment or maintenance chemotherapy is acceptable), (5) a home computer or smartphone with reliable Internet connection. YAs will be excluded for the following reasons: (1) evidence of a cancer recurrence, (2) history of multiple primary cancers, (3) currently receiving palliative or hospice care, or (4) significant psychiatric history.

Study Sites & Recruitment. Eligible YAs will be identified through cancer registries and electronic medical record review at two participating comprehensive cancer centers: the Wake Forest Baptist Comprehensive Cancer Center (WFBCCC) and the Robert H. Lurie Comprehensive Cancer Center (RHLCCC) of Northwestern University. Consent will be sought from patients’ providers to contact potential participants. Mailed recruitment letters will be sent to the address on file with follow-up calls placed within two weeks to non-responders. We will supplement this recruitment approach by disseminating study information via flyers, email blasts, and other postings to local community resources that address the needs of the YA community in the respective regions. Interested YAs will be directed to a recruitment website for additional information about the study and to complete a preliminary online screener on REDCap (Research Electronic Data Capture), a secure web application for building and managing online surveys and databases. Eligible YAs, identified by their responses to the online screener, will be navigated to the consent form and baseline questionnaire on REDCap.

The WFBCCC sees a high volume of YAs with cancer annually. In the last fiscal year, 901 YAs with cancer were seen and ~550 of those were post-treatment survivors. Similarly, 800 YAs were seen at the RHLCCC during that time with ~400 post-treatment survivors. Based on a conservative 13% recruitment rate, we would anticipate recruiting 352 YAs within 36 months. Given the typical patient demographics for YAs seen at both sites, we are expecting the following gender and racial/ethnic distributions: 62.3% female, 20.6% Hispanic/Latino, 12.7% Black/African-American. Accordingly, our recruitment plan is feasible and should result in a diverse sample with respect to gender and race/ethnicity. Should recruitment lag, we have partnered with a regional non-profit, Cancer Services, to help boost our recruitment efforts in the YA community in the greater Piedmont Triad area of western North Carolina (see *Lanford’s LOS*).

3.4.B. Procedures

Data Collection. Once consented, eligible participants will be given a unique study ID and PIN # to log-in and complete study questionnaires online through REDCap.^{133,134} The REDCap instrument library includes self-report batteries or profiles from Patient-Reported Outcomes Measurement Information System (PROMIS) and the NIH Toolbox which include many of the static short forms and computer adaptive tests (CATs) that will be used in the study. At completion of the baseline questionnaire, YAs will be randomized and given access to one of the 32 conditions designed to test individuals components from the EMPOWER intervention. The EMPOWER intervention will be hosted and managed by the Research Information Systems Unit at the Wake Forest University Health Sciences. The Research Information Systems Unit has an extensive history of developing and refining web-based resources for use in clinical trial management (See Facilities & Resources).

The EMPOWER intervention is a 5 session online intervention that teaches behavioral and cognitive skills for increasing psychological well-being: 1) noting daily positive events, capitalizing on or savoring positive events, and gratitude; 2) mindfulness; 3) positive reappraisal; 4) focusing on personal strengths, setting and working toward attainable goals; and 5) small acts of kindness. The skills are presented over the course of 5 weeks. A week will consist of 1-2 days of didactic material and several days of brief, real-life skills practice and reporting, with each day's "home practice" taking approximately 20-30 minutes to complete. YAs cannot skip ahead, but they can return to old lessons or exercises if they choose. Most exercises are done in a "diary" format in which YAs' past responses are displayed next to their new ones, so that every time they visit that exercise they see their growing list of past positive experiences. YAs will be permitted up to 8 weeks to complete this self-guided intervention to account for normal interruptions and unexpected delays in life. In addition to the baseline questionnaires (T1), YAs across all 32 conditions will complete 1-week (T2), 1-month (T3), 3-month (T4), and 6-month (T5) post-intervention follow-up questionnaires. YAs will be compensated \$20 for each assessment for a maximum total of \$100. All questionnaires will be completed via REDCap. For YAs who do not receive EMPOWER components or only receive some EMPOWER components, inert content will be programmed into the web-based intervention delivery and will also include lessons and "home practice." Inert content will be used as a credible intervention control¹³⁵ and to promote engagement among YAs. Inert content will cover journaling (writing about a typical day of the week and the things that happened during it, the facts about a problem, and how you spent your time or plan to spend your time during the week) and reading tasks (nutrition, the body's stress response). Evidence suggests these topics will be inert.¹³⁶⁻¹⁴⁰ If this assumption is incorrect and inert content increases psychological well-being, we will have underestimated EMPOWER effect sizes.

Outcomes: The primary outcomes for this study (Table 4) are measures of psychological well-being (depression, anxiety, positive affect, and life satisfaction). Psychological well-being will be assessed with NIH PROMIS CATs for depression and anxiety¹⁴¹ and NIH Toolbox CATs for positive affect and life satisfaction.⁹⁷ Secondary

Type/Purpose of Measure	Variable	Measures
Primary Outcomes	Psychological Well-Being	NIH PROMIS Depression CAT
		NIH PROMIS Anxiety CAT
		NIH Toolbox Positive Affect CAT
		NIH Toolbox Life Satisfaction CAT
Secondary Outcomes	Physical Well-Being	NIH PROMIS Physical Functioning CAT
		NIH PROMIS Fatigue CAT
	Social Well-Being	NIH PROMIS Satisfaction with Social Roles CAT
	Health Behaviors	HINTS - Diet Questions
		HINTS - Alcohol Use & Smoking Questions
		Leisure Time Exercise Questionnaire
Sedentary Activity Questionnaire		
Mediating Variables	Coping Self-Efficacy	NIH PROMIS Self-Efficacy - Managing Emotions CAT
	Social Support	NIH PROMIS Emotional Support CAT
Participant Characteristics	Demographics	Age, gender, race, ethnicity, education, income, etc.
	Clinical	Cancer diagnosis, stage, treatments, performance status

outcomes will be physical functioning, fatigue, satisfaction with social roles and responsibilities, and health behaviors. PROMIS CATs will be used for assessing YAs' physical functioning,¹⁴² fatigue,¹⁰¹ and satisfaction with social roles and responsibilities.¹⁴³ Healthy behaviors often associated with enhanced coping and better adjustment¹⁴⁴ will be assessed: diet,¹⁴⁵ exercise,¹⁴⁶ sedentary behavior,¹⁴⁷ alcohol consumption,¹⁴⁵ and cigarette smoking.¹⁴⁵ Potential mediating variables identified by Fredrickson's Broaden and Build Theory are coping self-efficacy and social support. We will administer the PROMIS Self-Efficacy for Managing Emotions and PROMIS Emotional Support CATs to assess these respective constructs.¹⁴⁸ All of the above measures have established reliability and validity and will be administered at all five time points. The primary outcomes will be assessed weekly during the intervention to allow us to separate the effects of the intervention components on the outcomes. Based on past data collection efforts, participants taking PROMIS measures typically complete questionnaires at a rate of 6 items per minute with more rapid completion times for web-based assessments.¹⁴⁹ A significant advantage of CAT lies in the tailored assessment which minimizes error in measurement (thus, yielding greater precision). Given the minimal response burden these measures pose to participants, the questionnaire battery should take <30 minutes on average to complete in REDCap with most YAs completing the battery in 15-20 minutes. Lastly, standard socio-demographic questions will be administered along with clinical questions at baseline in order to account for potential characteristics that might

impact outcomes.

3.4.C. Analysis

Analytic Plan for Aim 1. An estimated 2,850 YAs will be screened for eligibility over a three year period (1,650 at WFBCCC and 1,200 at RHLCCC). Our prior research indicates ~16.5% (23% at WFBCCC and 10% at RHLCCC) screened will be eligible and interested. Therefore, we can expect at least 352 YAs will be individually randomized to one of 32 experimental conditions (n=11 per condition, total n=352) after completing a baseline assessment. Randomization assignments will be administered and monitored by the study statistician, Dr. Tooze. Block randomization with block size 64 will be used to ensure balanced sample sizes at the end of the trial. The primary outcomes are psychological well-being (depression, anxiety, positive affect, and life satisfaction) scores at the 1 month follow-up (T3). The following additive model forms the basis of our power calculation as well as subsequent analyses:

$$Y_{FU} = \mu + \beta_0 Y_{PRE} + \beta_1 X_1 + \dots + \beta_5 X_5 + \varepsilon, \quad (1)$$

where Y (FU=follow up, PRE=pre-intervention) represents a psychological well-being outcome score, X_i represents the i th intervention component, μ represents an intercept, and ε represents random error. Equation (1) separates the outcome into the sum of effects of the intervention components. To evaluate interactions between intervention components, one can add interaction terms (e.g., $X_1 X_2$) to the model in (1). Significance tests will be conducted for the linear model in (1) to determine the effect size and statistical significance of the components. Separate longitudinal mixed effects linear models that include all observations will be fit with the psychological well-being scores as the dependent variables. Fixed effects will include variables for each intervention component, their interactions, pre-intervention well-being scores, and time (for assessing possible trends). The model will incorporate random effects to account for repeated measures on individuals. An autoregressive covariance matrix will be used to model the random effects. The main effects of each intervention component will be estimated from this model using contrasts. Due to randomization, we do not anticipate any differences in covariates between groups; however, we will evaluate differences by main effects and adjust for them if necessary. Stage at diagnosis and cancer type are not consistently associated with psychological distress in YAs,¹⁰ therefore we do not need to stratify or control for these variables.⁶⁰ Effect sizes for psychological well-being outcomes will be estimated using baseline standard deviations. Similar models will be fitted to examine secondary outcomes of physical well-being (physical functioning, fatigue), social well-being (satisfaction with social roles and activities), and health behavior (diet, exercise, sedentary behavior, alcohol and tobacco use).

Sample Size and Power Calculation. The MOST framework is a resource-efficient strategy that utilizes all participants to calculate main effects. Unlike a classical multi-arm randomized clinical trial, the full-factorial experiment preserves power, which is driven by the total sample size, not cell size.¹⁵⁰ Sample size estimates are based on the lowest anticipated effect size for intervention components, ensuring the sample size is adequate to detect larger effect sizes.²⁸ Antoni et al.¹⁵¹ found intervention effect sizes of 0.43–0.55 on emotional distress. Similar effect sizes were reported from eCBT interventions for various conditions.¹⁵² Psychosocial oncology interventions for breast cancer survivors reported similar effect sizes for anxiety.^{153–155} *Our pilot research suggests we can expect an effect size (mean difference/standard deviation) of approximately 0.50 among YAs and so this will be used as our criterion for retaining individual intervention components in the final optimized EMPOWER intervention.* Based on the MOST framework²⁸ presented in Figure 1, individual intervention components that demonstrate an effect during Step 3 are included in intervention assembly and confirmatory testing in Steps 4-5. Therefore, we have set alpha at 0.10 given our tolerance for Type I error because intervention components will go on for confirmatory testing. Power analysis for the full factorial experiment was based on a total of n=352 recruited participants and a 72% retention rate at 1-month follow-up (final n=256). The detectable effect size for a main effect is 0.31 (95% CI=(0.06, 0.56)) at 80% power. The detectable effect size for an interaction is 0.62 (95% CI=(0.37, 0.87)). This implies that the study has sufficient power to pinpoint an effective intervention component that is effective for inclusion into the optimized design. The study may not have sufficient power to detect small interaction (synergistic) effects (<0.62). The power analysis was conducted using the SAS macro FactorialPowerPlan.¹⁵⁶

3.5. AIM 2: Identify mediators and moderators of intervention components for well-being outcomes.

After identifying which components of EMPOWER are efficacious (Aim 1), we will examine mediators and moderators of the relationship between EMPOWER intervention components and our primary psychological well-being outcomes of positive affect, life satisfaction, depression, and anxiety. This will allow us to explore the potential mechanisms through which the EMPOWER intervention components impact outcomes (i.e., mediation) as well as the conditions under which the effect of the EMPOWER intervention components on psychological well-being varies (i.e., moderation). Consistent with the Broaden and Build Theory, we expect the intervention skills to improve coping self-efficacy and social support which will be two potential pathways (i.e., mediators) through which the EMPOWER intervention will impact psychological well-being.

3.5.A. Analysis

Analytic Plan for Aim 2. Mediation analyses aim to identify mediators of which influences can be associated precisely to particular, relatively discrete intervention components and their interactions.¹⁵⁷ We will analyze coping self-efficacy and social support as potential mediating variables. In other words, we will examine the degree to which the link between EMPOWER intervention components and well-being occurs through the influence of coping self-efficacy or social support. Mediation models will only include intervention components that are deemed to be effective and included in the subsequent RCT. The individual indirect effects of the mediators and total effect will be estimated. Moderation analyses will examine the interaction between the optimized intervention components and two potential moderators: age and gender. Mediation and moderation analyses will be conducted with MacKinnon et al.'s¹⁵⁸ and Aiken & West's¹⁵⁹ respective approaches.

3.6. Design Considerations

We deliberated about a number of design considerations in planning this study:

Why use post-treatment YAs and not on-treatment YAs for our target sample? There are 70,000 new diagnoses of YAs annually and an estimated 2 million YA survivors in 2018. Post-treatment YAs remain at risk of clinically significant distress and thus our approach to target post-treatment survivors' distress is an important intervention focus and more feasible given the number of YA survivors.

Why combine all cancer types instead of focusing only on a particular cancer type among YAs for the EMPOWER intervention? Kwak et al.¹⁰ demonstrated that psychological distress is independent of cancer type and stage for YAs. Since our primary endpoint is psychological well-being (inclusive of common distress endpoints), it is appropriate to combine all cancer types. This also enhances the feasibility of recruitment.

Why use "disease agnostic" PROMIS measures instead of cancer-specific measures for this study? Given the developmental and disease heterogeneity of YAs we needed to use measures that would give us maximum flexibility in assessment without sacrificing measurement precision. The calibrated item banks of the NIH PROMIS and NIH Toolbox meet this criteria. We can administer computer adaptive tests for optimum flexibility without undue participant burden. Moreover, the T-scores provide valuable reference points for determination of clinical significance of scores and meaningful change.

Why not recruit YAs from community sites instead of comprehensive cancer centers? Presumably, YAs from community sites would be a more representative sample. We have established relationships with the RHLCCC and WFBCCC and pilot feasibility and acceptability data. Given the high volume of YAs seen annually at these two sites, it is prudent to use samples from these sites for intervention optimization (Aim 1). Although most YAs are treated in community based practices and not in academic medical centers, based on the demographic and clinical variables of potentially eligible YAs at RHLCCC and WFBCCC, we do not expect significant differences for those characteristics compared to if we had recruited YAs through community-based practices. Moreover, we are planning to recruit through community-based practices by leveraging the ECOG-ACRIN NCI Community Oncology Research Program (NCORP) as part of a subsequent R01 designed to conduct a large, multi-site RCT to test the optimized EMPOWER intervention to demonstrate clinical and cost-effectiveness.

3.7. Study Timeline

Table 5: Four Year Project Timeline	Year 1				Year 2				Year 3				Year 4			
Study Task	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Study start-up	X	X														
Aim 1: Optimization		X	X	X	X	X	X	X	X	X	X	X	X	X		
Aim 1 & 2: Data Analysis									X	X	X	X	X	X	X	
Aim 1 & 2: Abstract/Manuscript writing											X	X	X	X	X	X
Follow-up R01 Grant writing														X	X	X

3.8. Future Directions

Upon completion of this four-year study, we will have efficacy data to inform a fully optimized intervention (EMPOWER) to improve psychological well-being among YA cancer survivors by reducing distress (depression and anxiety) and enhancing well-being (positive affect and life satisfaction). Moreover, we will be well-positioned to submit a much larger, multi-site RCT by leveraging the NCI Community Oncology Research Program (NCORP). This subsequent R01 submission would serve as the confirmatory RCT of our web-based, scalable EMPOWER intervention and will be ideally-suited for YAs who would otherwise not have access to supportive care interventions to help manage post-treatment distress and enhance well-being.

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