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).

Accessibility
Individuals using assistive technology (e.g., screen reader, Braille reader) who experience difficulty accessing any information should send an email to the Healthcare Delivery Research Program (NCIHDRP@mail.nih.gov).

424 R&R and PHS-398 Specific
Table Of Contents

Examples of Funded Grants in Healthcare Delivery Research	1
Table Of Contents	2
SF 424 R&R Face Page	3
Project Summary	4
Project Narrative	5
Specific Aims	6
1. Significance	7
2. Innovation	10
3. Approach	10
References	20

SF 424 R&R Face Page

PI: Salsman, John

Grant Number: 1 R01 CA242849-01

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 samples[20-24]), unique from the influence of distress, and includes domains that are inherently valued by patients (better relationships, more creativity, and better work quality[25]).

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 Theory[26] and Revised Stress and Coping Theory[27], 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 survivors[46] 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 Theory[27] 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" argument[66] – 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 way[62] 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 management[67], cognitive-behavioral therapy plus hypnosis[68], supportive expressive group therapy[69], expressive writing[70], 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 activity[76], weight loss[77] 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 rate[83] 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 communication[85-87] 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 smartphones[88] 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 tosupportive 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 Toolbox[96-98] 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 psychotherapy[104] 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]

Table 2. Overview of the Skills and Content of the EMPOWER Intervention

Session	Skills	Session Content
Week 1	1. Positive events	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. Capitalizing	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. Gratitude	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	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. Achievable Goals	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)

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 illness[120] 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]

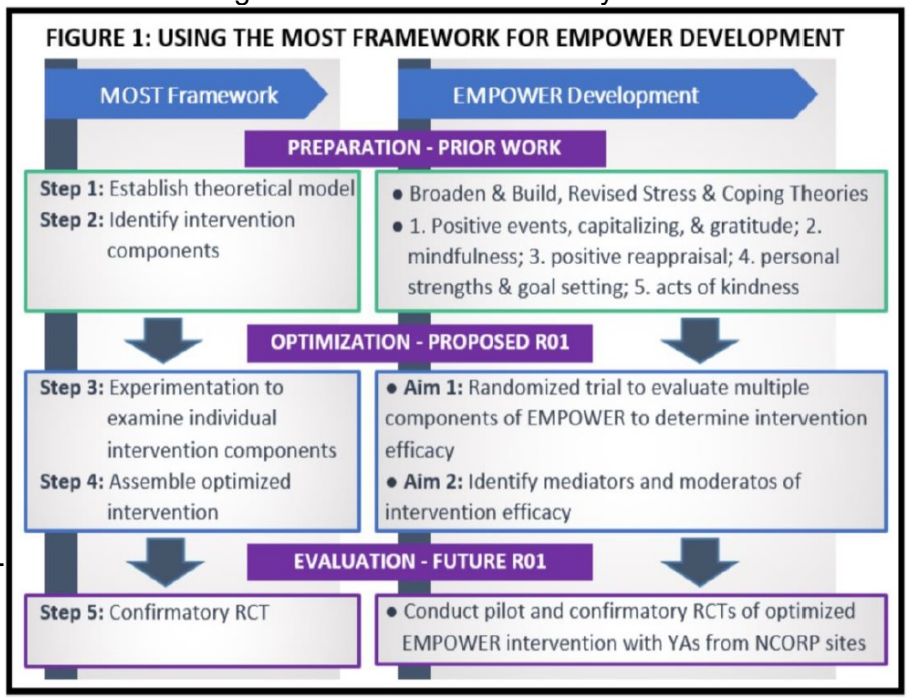
Altruistic Behaviors/Acts of Kindness (Week 5). Volunteerism and other altruistic behaviors are associated with lower risk of mortality[125,126] and lower risk of serious illness[127] in large representative samples. Altruistic behavior may be associated with psychological well-being because it distracts one from his/her own problems, increases self-esteem, or increases a sense of mastery or general self-efficacy.[128]

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 (Ps>.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 Build[26] and Revised Stress and Coping Theories[118] 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 (2^5). 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

Table 3: Full Factorial Design for EMPOWER

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 control[135] 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 anxiety[141] and NIH Toolbox CATs for positive affect and life satisfaction.[97] Secondary 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 adjustment[144] 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

Table 4: Study Measures

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

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:

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

where Y (FU=follow up, PRE=pre-intervention) represents a psychological well-being outcome score, X_i represents the ith 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_1X_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 framework[28] 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.'s[158] and Aiken & West's[159] 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.

References

1. National Cancer Institute. A Snapshot of Adolescent and Young Adult Cancers: Cancers Affecting Adolescents and Young Adults (AYAs). 2014; https://www.cancer.gov/research/progress/snapshots/adolescent-young-adult. Accessed Sept. 22, 2016.
2. Barr RD, Ferrari A, Ries L, Whelan J, Bleyer WA. Cancer in Adolescents and Young Adults: A Narrative Review of the Current Status and a View of the Future. *JAMA pediatrics.* 2016;170(5):495-501.
3. The World Bank. Life expectancy at birth, total (years). http://data.worldbank.org/indicator/SP.DYN.LE00.IN. Accessed November 1, 2018.
4. Moskowitz JT. Coping interventions and the regulation of positive affect. In: Folkman S, ed. *The Oxford handbook of stress, health, and coping.* Oxford; New York: Oxford University Press; 2011.
5. Zebrack B. Information and service needs for young adult cancer survivors. *Support Care Cancer.* 2009;17(4):349-357.
6. Zebrack BJ. Psychological, social, and behavioral issues for young adults with cancer. *Cancer.* 2011;117(10):2289-2294.
7. Smith AW, Parsons HM, Kent EE, et al. Unmet Support Service Needs and Health-Related Quality of Life among Adolescents and Young Adults with Cancer: The AYA HOPE Study. *Frontiers in oncology.* 2013;3:75.
8. Guy GP, Jr., Yabroff KR, Ekwueme DU, et al. Estimating the health and economic burden of cancer among those diagnosed as adolescents and young adults. *Health Aff (Millwood).* 2014;33(6):1024- 1031.
9. Yanez B, Garcia S, Victorson D, Salsman JM. Distress among young adult cancer survivors: a cohort study. *Support Care Cancer.* 2013;21(9):2403-2408.
10. Kwak M, Zebrack BJ, Meeske KA, et al. Trajectories of Psychological Distress in Adolescent and Young Adult Patients With Cancer: A 1-Year Longitudinal Study. *J Clin Oncol.* 2013;31(17):2160-2166.
11. Landwehr MS, Watson SE, Macpherson CF, Novak KA, Johnson RH. The cost of cancer: a retrospective analysis of the financial impact of cancer on young adults. *Cancer medicine.* 2016.
12. Baker KS, Ambrose K, Arvey SR, et al. Financial and work related impact of cancer in young adult (YA) survivors. Paper presented at: ASCO Annual Meeting Proceedings2016.
13. Smith AW, Seibel NL, Lewis DR, et al. Next steps for adolescent and young adult oncology workshop: An update on progress and recommendations for the future. *Cancer.* 2016;122(7):988-999.
14. Barnett M, McDonnell G, DeRosa A, et al. Psychosocial outcomes and interventions among cancer survivors diagnosed during adolescence and young adulthood (AYA): a systematic review. *J Cancer Surviv.* 2016;10(5):814-831.
15. Walker E, Martins A, Aldiss S, Gibson F, Taylor RM. Psychosocial Interventions for Adolescents and Young Adults Diagnosed with Cancer During Adolescence: A Critical Review. *J Adolesc Young Adult Oncol.* 2016;5(4):310-321.
16. Kato PM, Cole SW, Bradlyn AS, Pollock BH. A video game improves behavioral outcomes in adolescents and young adults with cancer: a randomized trial. *Pediatrics.* 2008;122(2):e305-317.
17. Valle CG, Tate DF, Mayer DK, Allicock M, Cai J. A randomized trial of a Facebook-based physical activity intervention for young adult cancer survivors. *J Cancer Surviv.* 2013;7(3):355-368.
18. Rabin C, Simpson N, Morrow K, Pinto B. Intervention format and delivery preferences among young adult cancer survivors. *Int J Behav Med.* 2013;20(2):304-310.
19. Pressman SD, Cohen S. Does positive affect influence health? *Psychol Bull.* 2005;131(6):925-971.
20. Chida Y, Steptoe A. Positive Psychological Well-Being and Mortality: A Quantitative Review of Prospective Observational Studies. *Psychosom Med.* 2008;70(7):741-756.
21. Moskowitz JT. Positive Affect Predicts Lower Risk of AIDS Mortality. *Psychosom Med.* 2003;65(4):620.
22. Steptoe A, Wardle J. Positive affect measured using ecological momentary assessment and survival in older men and women. *Proc Natl Acad Sci.* 2011;108(45):18244–18248.
23. Moskowitz JT, Acree M, Epel ES. Positive Affect Uniquely Predicts Lower Risk of Mortality in People With Diabetes. *Health Psychol.* 2008;27(1 Suppl.):S73-S82.
24. Liu B, Floud S, Pirie K, Green J, Peto R, Beral V. Does happiness itself directly affect mortality? The prospective UK Million Women Study. *Lancet.* 2016;387(10021):874-881.
25. Lyubomirsky S, King L, Diener E. The benefits of frequent positive affect: does happiness lead to success? *Psychol Bull.* 2005;131(6):803-855.
26. Fredrickson BL. The Role of Positive Emotions in Positive Psychology: The Broaden-and-Build Theory of

Positive Emotions. *Am Psychol.* 2001;56(3):218-226.
27. Folkman S. The case for positive emotions in the stress process. *Anxiety Stress Coping.* 2008;21(1):3-14.
28. Collins LM, Baker TB, Mermelstein RJ, et al. The multiphase optimization strategy for engineering effective tobacco use interventions. *Ann Behav Med.* 2011;41(2):208-226.
29. Collins LM, Kugler KC, Gwadz MV. Optimization of Multicomponent Behavioral and Biobehavioral Interventions for the Prevention and Treatment of HIV/AIDS. *AIDS Behav.* 2016;20 Suppl 1:S197-214.
30. U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute, LIVESTRONG™ Young Adult Alliance. Closing the gap: research and care imperatives for adolescents and young adults with cancer. 2006; http://planning.cancer.gov/library/AYAO_PRG_Report_2006_FINAL.pdf. Accessed April 6, 2008.
31. Keegan THM, Ries LAG, Barr RD, et al. Comparison of cancer survival trends in the United States of adolescents and young adults with those in children and older adults. *Cancer.* 2016;122(7):1009-1016.
32. Bellizzi KM, Smith A, Schmidt S, et al. Positive and negative psychosocial impact of being diagnosed with cancer as an adolescent or young adult. *Cancer.* 2012;118(20):5155-5162.
33. Ries L, Trama A, Nakata K, Gatta G, Botta L, Bleyer A. Cancer Incidence, Survival, and Mortality Among Adolescents and Young Adults. In: *Cancer in Adolescents and Young Adults.* Springer; 2017:7- 42.
34. Fidler MM, Gupta S, Soerjomataram I, Ferlay J, Steliarova-Foucher E, Bray F. Cancer incidence and mortality among young adults aged 20-39 years worldwide in 2012: a population-based study. *Lancet Oncol.* 2017;18(12):1579-1589.
35. Park EM, Rosenstein DL. Depression in adolescents and young adults with cancer. *Dialogues Clin Neurosci.* 2015;17(2):171.
36. Sansom-Daly UM, Wakefield CE. Distress and adjustment among adolescents and young adults with cancer: an empirical and conceptual review. *Translational pediatrics.* 2013;2(4):167-197.
37. Muffly LS, Hlubocky FJ, Khan N, et al. Psychological morbidities in adolescent and young adult blood cancer patients during curative-intent therapy and early survivorship. *Cancer.* 2016;122(6):954-961.
38. Sheppard VB, Harper FW, Davis K, Hirpa F, Makambi K. The importance of contextual factors and age in association with anxiety and depression in Black breast cancer patients. *Psychooncology.* 2014;23(2):143-150.
39. Lang MJ, David V, Giese-Davis J. The Age Conundrum: A Scoping Review of Younger Age or Adolescent and Young Adult as a Risk Factor for Clinical Distress, Depression, or Anxiety in Cancer. *J Adolesc Young Adult Oncol.* 2015;4(4):157-173.
40. National Cancer Institute, LIVESTRONG™ Young Adult Alliance. Closing the gap: a strategic plan. Addressing the recommendations of the Adolescent and Young Adult Oncology Progress Review Group. 2006; http://planning.cancer.gov/library/2007_ayao_SP.pdf. Accessed October 29, 2012.
41. Coccia PF, Altman J, Bhatia S, et al. Adolescent and young adult oncology. Clinical practice guidelines in oncology. *J Natl Compr Canc Netw.* 2012;10(9):1112-1150.
42. Coccia PF, Pappo AS, Altman J, et al. Adolescent and young adult oncology, version 2.2014. *J Natl Compr Canc Netw.* 2014;12(1):21-32; quiz 32.
43. Weiss AR, Nichols CR, Freyer DR. Enhancing Adolescent and Young Adult Oncology Research Within the National Clinical Trials Network: Rationale, Progress, and Emerging Strategies. *Semin Oncol.* 2015;42(5):740-747.
44. Nass SJ, Beaupin LK, Demark-Wahnefried W, et al. Identifying and addressing the needs of adolescents and young adults with cancer: summary of an Institute of Medicine workshop. *Oncologist.* 2015;20(2):186-195.
45. National Cancer Policy Forum. In: *Identifying and Addressing the Needs of Adolescents and Young Adults with Cancer: Workshop Summary.* Washington (DC): National Academies Press (US); 2014.
46. Bloom JR, Stewart SL, D'Onofrio CN, Luce J, Banks PJ. Addressing the needs of young breast cancer survivors at the 5 year milestone: can a short-term, low intensity intervention produce change? *J Cancer Surviv.* 2008;2(3):190-204.
47. Moskowitz JT, Carrico AW, Duncan LG, et al. Randomized controlled trial of a positive affect intervention for people newly diagnosed with HIV. *J Consult Clin Psychol.* 2017;85(5):409-423.
48. Cohn MA, Pietrucha ME, Saslow LR, Hult JR, Moskowitz JT. An online positive affect skills intervention reduces depression in adults with type 2 diabetes. *The journal of positive psychology.* 2014;9(6):523-534.
49. Moskowitz JT, Cheung EO, Snowberg K, et al. Randomied controlled trial of a facilitated online positive

emotion regulation intervention for dementia caregivers. *Health psychology : official journal of the Division of Health Psychology, American Psychological Association.* in press.
50. Cheung EO, Cohn MA, Dunn LB, et al. A randomized pilot trial of a positive affect skill intervention (lessons in linking affect and coping) for women with metastatic breast cancer. *Psychooncology.* 2016.
51. Samman E. Psychological and subjective wellbeing: a proposal for internationally comparable indicators. *Oxford Development Studies.* 2007;35(4):459-486.
52. Diener E, Suh EM, Lucas RE, Smith HL. Subjective Well-Being: Three Decades of Progress. *Psychol Bull.* 1999;125(2):276-302.
53. Diener E. Subjective well-being. *Psychol Bull.* 1984;95(3):542-575.
54. Cohen S, Pressman SD. Positive Affect and Health. *Curr Dir Psychol Sci.* 2006;15(3):122-125.
55. Danner DD, Snowdon DA, Friesen WV. Positive emotions in early life and longevity: findings from the nun study. *J Pers Soc Psychol.* 2001;80(5):804-813.
56. Fredrickson BL, Levenson RW. Positive Emotions Speed Recovery from the Cardiovascular Sequelae of Negative Emotions. *Cogn Emot.* 1998;12(2):191-220.
57. Richman LS, Kubzansky L, Maselko J, Kawachi I, Choo P, Bauer M. Positive emotion and health: going beyond the negative. *Health Psychol.* 2005;24(4):422-429.
58. Diener E. Subjective well-being. The science of happiness and a proposal for a national index. *Am Psychol.* 2000;55(1):34-43.
59. Koizumi M, Ito H, Kaneko Y, Motohashi Y. Effect of having a sense of purpose in life on the risk of death from cardiovascular diseases. *J Epidemiol.* 2008;18(5):191-196.
60. Verduin PJ, de Bock GH, Vliet Vlieland TP, Peeters AJ, Verhoef J, Otten W. Purpose in life in patients with rheumatoid arthritis. *Clin Rheumatol.* 2008;27(7):899-908.
61. Mascaro N, Rosen DH. Existential meaning's role in the enhancement of hope and prevention of depressive symptoms. *J Pers.* 2005;73(4):985-1013.
62. Lyubomirsky S, Sheldon KM, Schkade D. Pursuing happiness: The architecture of sustainable change. *Rev Gen Psychol.* 2005;9(2):111-131.
63. Braungart JM, Plomin R, DeFries JC, Fulker DW. Genetic influence on tester-rated infant temperament as assessed by Bayley's Infant Behavior Record: Nonadoptive and adoptive siblings and twins. *Dev Psychol.* 1992;28(1):40.
64. Tellegen A, Lykken DT, Bouchard TJ, Jr., Wilcox KJ, Segal NL, Rich S. Personality similarity in twins reared apart and together. *J Pers Soc Psychol.* 1988;54(6):1031-1039.
65. Brickman P, Coates D, Janoff-Bulman R. Lottery winners and accident victims: is happiness relative? *J Pers Soc Psychol.* 1978;36(8):917-927.
66. Diener E, Lucas RE, Scollon CN. Beyond the hedonic treadmill: revising the adaptation theory of well-being. *Am Psychol.* 2006;61(4):305.
67. Antoni MH, Lechner SC, Kazi A, et al. How stress management improves quality of life after treatment for breast cancer. *J Consult Clin Psychol.* 2006;74(6):1143-1152.
68. Schnur JB, David D, Kangas M, Green S, Bovbjerg DH, Montgomery GH. A randomized trial of a cognitive-behavioral therapy and hypnosis intervention on positive and negative affect during breast cancer radiotherapy. *J Clin Psychol.* 2009;65(4):443-455.
69. Giese-Davis J, DiMiceli S, Sephton S, Spiegel D. Emotional expression and diurnal cortisol slope in women with metastatic breast cancer in supportive-expressive group therapy: a preliminary study. *Biol Psychol.* 2006;73(2):190-198.
70. Lu Q, Zheng D, Young L, Kagawa-Singer M, Loh A. A pilot study of expressive writing intervention among Chinese-speaking breast cancer survivors. *Health Psychol.* 2012;31(5):548-551.
71. Vadiraja HS, Rao MR, Nagarathna R, et al. Effects of yoga program on quality of life and affect in early breast cancer patients undergoing adjuvant radiotherapy: a randomized controlled trial. *Complement Ther Med.* 2009;17(5-6):274-280.
72. Danhauer SC, Mihalko SL, Russell GB, et al. Restorative yoga for women with breast cancer: findings from a randomized pilot study. *Psychooncology.* 2009;18(4):360-368.
73. Badger TA, Segrin C, Figueredo AJ, et al. Who benefits from a psychosocial counselling versus educational intervention to improve psychological quality of life in prostate cancer survivors? *Psychol Health.* 2013;28(3):336-354.
74. Strecher VJ, McClure J, Alexander G, et al. The role of engagement in a tailored web-based smoking cessation program: randomized controlled trial. *J Med Internet Res.* 2008;10(5):e36.
75. Strecher VJ, McClure JB, Alexander GL, et al. Web-based smoking-cessation programs: results of a

randomized trial. *Am J Prev Med.* 2008;34(5):373-381.
76. Phillips SM, Collins LM, Penedo FJ, et al. Optimization of a technology-supported physical activity intervention for breast cancer survivors: Fit2Thrive study protocol. *Contemp Clin Trials.* 2018;66:9-19.
77. Pellegrini CA, Hoffman SA, Collins LM, Spring B. Optimization of remotely delivered intensive lifestyle treatment for obesity using the Multiphase Optimization Strategy: Opt-IN study protocol. *Contemp Clin Trials.* 2014;38(2):251-259.
78. Wagner LI, Duffecy J, Penedo F, Mohr DC, Cella D. Coping strategies tailored to the management of fear of recurrence and adaptation for E-health delivery: The FoRtitude intervention. *Cancer.* 2017;123(6):906-910.
79. Oh H, Rizo C, Enkin M, Jadad A. What is eHealth?: a systematic review of published definitions. *World Hosp Health Serv.* 2005;41(1):32-40.
80. Tufano JT, Karras BT. Mobile eHealth interventions for obesity: a timely opportunity to leverage convergence trends. *J Med Internet Res.* 2005;7(5):e58.
81. Ruland CM, Maffei RM, Borosund E, Krahn A, Andersen T, Grimsbo GH. Evaluation of different features of an eHealth application for personalized illness management support: cancer patients' use and appraisal of usefulness. *Int J Med Inform.* 2013;82(7):593-603.
82. Linn AJ, Vervloet M, van Dijk L, Smit EG, Van Weert JC. Effects of eHealth interventions on medication adherence: a systematic review of the literature. *J Med Internet Res.* 2011;13(4):e103.
83. Mertz L. Ultrasound? Fetal monitoring? Spectrometer? There's an app for that!: biomedical smart phone apps are taking healthcare by storm. *IEEE Pulse.* 2012;3(2):16-21.
84. Doherty ST, Oh P. A multi-sensor monitoring system of human physiology and daily activities. *Telemed J E Health.* 2012;18(3):185-192.
85. Kreps GL, Neuhauser L. New directions in eHealth communication: Opportunities and challenges. *Patient Educ Couns.* 2010;78(3):329-336.
86. Suggs LS, McIntyre C. Are we there yet? An examination of online tailored health communication. *Health Educ Behav.* 2009;36(2):278-288.
87. Rimer BK, Kreuter MW. Advancing Tailored Health Communication: A Persuasion and Message Effects Perspective. *Journal of Communication.* 2006;56:S184-S201.
88. Pew Research Center: Internet ST. Mobile Fact Sheet. 2017; http://www.pewinternet.org/fact-sheet/mobile/. Accessed February 2, 2017.
89. Pew Research Center: Internet ST. Internet/Broadband Fact Sheet. 2017; http://www.pewinternet.org/fact-sheet/internet-broadband/. Accessed February 2, 2017.
90. Salsman JM, Moskowitz JT, Park CL, Merluzzi TV. Promoting psychological well-being in cancer patients and survivors: Meta-analyses of randomized clinical trials. *Ann Behav Med.* 2017;51.
91. Katz MR, Irish JC, Devins GM. Development and pilot testing of a psychoeducational intervention for oral cancer patients. *Psychooncology.* 2004;13(9):642-653.
92. Kissane DW, Bloch S, Smith GC, et al. Cognitive-existential group psychotherapy for women with primary breast cancer: a randomised controlled trial. *Psychooncology.* 2003;12(6):532-546.
93. Manne SL, Kissane DW, Nelson CJ, Mulhall JP, Winkel G, Zaider T. Intimacy-enhancing psychological intervention for men diagnosed with prostate cancer and their partners: A pilot study. *J Sex Med.* 2011;8(4):1197-1209.
94. Manne S, Ostroff JS, Winkel G. Social-cognitive processes as moderators of a couple-focused group intervention for women with early stage breast cancer. *Health Psychol.* 2007;26(6):735-744.
95. Zebrack B, Mathews-Bradshaw B, Siegel S. Quality cancer care for adolescents and young adults: a position statement. *J Clin Oncol.* 2010;28(32):4862-4867.
96. Gershon RC, Bleck TP, Nowinski CJ. NIH Toolbox for Assessment of Neurological and Behavioral Function. *Neurology.* 2013;80(11 Supplement 3):S2-S6.
97. Salsman J, Lai J-S, Hendrie H, et al. Assessing psychological well-being: self-report instruments for the NIH Toolbox. *Qual Life Res.* 2014;23(1):205-215.
98. Salsman JM, Butt Z, Pilkonis PA, et al. Emotion assessment using the NIH Toolbox. *Neurology.* 2013;80(11 Supplement 3):S76-S86.
99. Cella D, Reeve B, Amtmann D, Hays R, Gershon R. The patient reported outcomes management information system (PROMIS); a cooperative effort to advance and enable clinical research. Paper presented at: International Society for Quality of Life Research; October 10-14, 2006; Lisbon, Portugal.
100. Cella D, Riley W, Stone A, et al. Initial adult health item banks and first wave testing of the Patient-Reported Outcomes Measurement Information System (PROMIS™) Network: 2005–2008. *J Clin*

Epidemiol. 2010;63(11):1179.
101. Garcia SF, Cella D, Clauser SB, et al. Standardizing patient-reported outcomes assessment in cancer clinical trials: a patient-reported outcomes measurement information system initiative. *J Clin Oncol.* 2007;25(32):5106-5112.
102. Salsman JM, Sorkin M, Cohn M, Steffen LE, Moskowitz JT. A web-based positive emotions intervention for young adult cancer survivors: Preliminary results from the EMPOWER study. *Psychooncology.* 2017;26.
103. Salsman JM, Steffen LE, Cohn MA, et al. Pilot testing of an online intervention to enhance psychological well-being in young adult cancer survivors: The EMPOWER trial. . Annual Conference of the Society of Behavioral Medicine; March 8, 2019, 2019; Washington, D.C.
104. Seligman ME, Rashid T, Parks AC. Positive psychotherapy. *Am Psychol.* 2006;61(8):774-788.
105. Murrell SA, Norris FH. Resources, life events, and changes in positive affect and depression in older adults. *Am J Community Psychol.* 1984;12(4):445-464.
106. Zautra AJ, Reich JW. Life events and perceptions of life quality: Developments in a two-factor approach. *J Community Psychol.* 1983;11(2):121-132.
107. Krause N. Positive life events and depressive symptoms in older adults. *Behav Med.* 1988;14(3):101-112.
108. Lewinsohn PM, Clarke GN, Hoberman HM. The Coping With Depression Course: Review and future directions. *Canadian Journal of Behavioural Science/Revue canadienne des sciences du comportement.* 1989;21(4):470.
109. Langston CA. Capitalizing on and coping with daily-life events: Expressive responses to positive events. *J Pers Soc Psychol.* 1994;67(6):1112.
110. Emmons RA. *Thanks! How the new science of gratitude can make you happier.* Houghton Mifflin Harcourt; 2007.
111. Emmons RA, McCullough ME. Counting blessings versus burdens: an experimental investigation of gratitude and subjective well-being in daily life. *J Pers Soc Psychol.* 2003;84(2):377-389.
112. Kashdan TB, Uswatte G, Julian T. Gratitude and hedonic and eudaimonic well-being in Vietnam war veterans. *Behav Res Ther.* 2006;44(2):177-199.
113. Kabat-Zinn J. Mindfulness-based interventions in context: past, present, and future. *Clinical psychology: Science and practice.* 2003;10(2):144-156.
114. Brown KW, Ryan RM. The benefits of being present: mindfulness and its role in psychological well-being. *J PersSoc Psychol.* 2003;84(4):822-848.
115. Grossman P, Tiefenthaler-Gilmer U, Raysz A, Kesper U. Mindfulness training as an intervention for fibromyalgia: evidence of postintervention and 3-year follow-up benefits in well-being. *Psychother Psychosom.* 2007;76(4):226-233.
116. Fredrickson BL, Cohn MA, Coffey KA, Pek J, Finkel SM. Open hearts build lives: positive emotions, induced through loving-kindness meditation, build consequential personal resources. *J Pers Soc Psychol.* 2008;95(5):1045-1062.
117. Lazarus RS, Folkman S. *Stress, appraisal, and coping.* New York: Springer Publishing Co.; 1984.
118. Folkman S. Positive psychological states and coping with severe stress. *Soc Sci Med.* 1997;45(8):1207-1221.
119. Sears SR, Stanton AL, Danoff-Burg S. The yellow brick road and the emerald city: Benefit finding, positive reappraisal coping and posttraumatic growth in women with early-stage breast cancer. *Health Psychol.* 2003;22(5):487-497.
120. Taylor SE, Collins RL, Skokan LA, Aspinwall LG. Maintaining positive illusions in the face of negative information: Getting the facts without letting them get to you. *Journal of Social and Clinical Psychology.* 1989;8(2):114-129.
121. Taylor SE, Lerner JS, Sherman DK, Sage RM, McDowell NK. Are self-enhancing cognitions associated with healthy or unhealthy biological profiles? *J Pers Soc Psychol.* 2003;85(4):605-615.
122. Carver CS, Scheier MF. Origins and functions of positive and negative affect: A control-process view. *Psychol Rev.* 1990;97(1):19-35.
123. Lent RW, Singley D, Sheu H-B, et al. Social cognitive predictors of domain and life satisfaction: Exploring the theoretical precursors of subjective well-being. *J Couns Psychol.* 2005;52(3):429.
124. Emmons RA. Abstract versus concrete goals: Personal striving level, physical illness, and psychological well-being. *J Pers Soc Psychol.* 1992;62(2):292-300.
125. Musick MA, Wilson J. Volunteering and depression: the role of psychological and social resources in

different age groups. *Soc Sci Med.* 2003;56(2):259-269.
126. Oman D, Thoresen CE, McMahon K. Volunteerism and Mortality among the Community-dwelling Elderly. *J Health Psychol.* 1999;4(3):301-316.
127. Moen P, Dempster-McClain D, Robin M. Williams J. Successful Aging: A Life-Course Perspective on Women's Multiple Roles and Health. *Am J Sociol.* 1992;97(6):1612-1638.
128. Penner LA, Dovidio JF, Piliavin JA, Schroeder DA. Prosocial behavior: multilevel perspectives. *Annu Rev Psychol.* 2005;56:365-392.
129. Parsons HM, Harlan LC, Seibel NL, Stevens JL, Keegan TH. Clinical trial participation and time to treatment among adolescents and young adults with cancer: does age at diagnosis or insurance make a difference? *J Clin Oncol.* 2011;29(30):4045-4053.
130. Collins CL, Malvar J, Hamilton AS, Deapen DM, Freyer DR. Case-linked analysis of clinical trial enrollment among adolescents and young adults at a National Cancer Institute-designated comprehensive cancer center. *Cancer.* 2015;121(24):4398-4406.
131. Sanford SD, Beaumont JL, Snyder MA, Reichek J, Salsman JM. Clinical research participation among adolescent and young adults at an NCI-designated Comprehensive Cancer Center and affiliated pediatric hospital. *Support Care Cancer.* 2017;25(5):1579-1586.
132. Downs-Canner S, Shaw PH. A comparison of clinical trial enrollment between adolescent and young adult (AYA) oncology patients treated at affiliated adult and pediatric oncology centers. *J Pediatr Hematol Oncol.* 2009;31(12):927-929.
133. REDCap Consortium. REDCap (Research Electronic Data Capture) Consortium. 2012; http://project-redcap.org/. Accessed January 17, 2012.
134. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)-A metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform.* 2009;42(2):377-381.
135. Christensen H, Griffiths KM, Jorm AF. Delivering interventions for depression by using the internet: randomised controlled trial. *BMJ.* 2004;328(7434):265.
136. Sheldon KM, Lyubomirsky S. How to increase and sustain positive emotion: The effects of expressing gratitude and visualizing best possible selves. *The journal of positive psychology.* 2006;1(2):73-82.
137. Kabat-Zinn J. *Full Catastrophe Living: Using the Wisdom of your Mind to Face Stress, Pain and Illness.* New York: Dell Publishing; 1990.
138. Stanton AL, Danoff-Burg S, Sworowski LA, et al. Randomized, controlled trial of written emotional expression and benefit finding in breast cancer patients. *J Clin Oncol.* 2002;20(20):4160-4168.
139. Baikie KA, Geerligs L, Wilhelm K. Expressive writing and positive writing for participants with mood disorders: an online randomized controlled trial. *J Affect Disord.* 2012;136(3):310-319.
140. Schueller SM, Parks AC. Disseminating self-help: positive psychology exercises in an online trial. *J Med Internet Res.* 2012;14(3):e63.
141. Pilkonis PA, Choi SW, Reise SP, Stover AM, Riley WT, Cella D. Item banks for measuring emotional distress from the Patient-Reported Outcomes Measurement Information System (PROMIS):depression, anxiety, and anger. *Assessment.* 2011;18(3):263-283.
142. Fries JF, Cella D, Rose M, Krishnan E, Bruce B. Progress in assessing physical function in arthritis: PROMIS short forms and computerized adaptive testing. *J Rheumatol.* 2009;36(9):2061-2066.
143. Cook KF, Bamer AM, Amtmann D, Molton IR, Jensen MP. Six Patient-Reported Outcome Measurement Information System Short Form Measures Have Negligible Age- or Diagnosis-Related Differential Item Functioning in Individuals With Disabilities. *Arch Phys Med Rehabil.* 2012;Epub ahead of print.
144. Doyle C, Kushi LH, Byers T, et al. Nutrition and Physical Activity During and After Cancer Treatment: An American Cancer Society Guide for Informed Choices. *CA.* 2006;56(6):323.
145. Nelson DE, Kreps GL, Hesse BW, et al. The Health Information National Trends Survey (HINTS): development, design, and dissemination. *J Health Commun.* 2004;9(5):443-460; discussion 481-444.
146. Godin G, Shephard RJ. A simple method to assess exercise behavior in the community. *Can J Appl Sport Sci.* 1985;10(3):141-146.
147. Marshall AL, Miller YD, Burton NW, Brown WJ. Measuring total and domain-specific sitting: a study of reliability and validity. *Med Sci Sports Exerc.* 2010;42(6):1094-1102.
148. HealthMeasures. HealthMeasures: Transforming how health is measured. 2017; http://www.healthmeasures.net/index.php. Accessed January 18, 2017.
149. Hays R, Bode R, Rothrock N, Riley W, Cella D, Gershon R. The impact of next and back buttons on time to complete and measurement reliability in web-based surveys *Qual Life Res.* 2010;19(8):1181– 1184.

150. Collins LM, Murphy SA, Strecher V. The multiphase optimization strategy (MOST) and the sequential multiple assignment randomized trial (SMART): new methods for more potent eHealth interventions. *Am J Prev Med.* 2007;32(5 Suppl):S112-118.
151. Antoni MH, Wimberly SR, Lechner SC, et al. Reduction of cancer-specific thought intrusions and anxiety symptoms with a stress management intervention among women undergoing treatment for breast cancer. *The American Journal of Psychiatry.* 2006;163(10):1791-1797.
152. Cuijpers P, van Straten A, Andersson G. Internet-administered cognitive behavior therapy for health problems: a systematic review. *J Behav Med.* 2008;31(2):169-177.
153. Jacobsen PB, Jim HS. Psychosocial interventions for anxiety and depression in adult cancer patients: achievements and challenges. *CA Cancer J Clin.* 2008;58(4):214-230.
154. Tatrow K, Montgomery GH. Cognitive behavioral therapy techniques for distress and pain in breast cancer patients: a meta-analysis. *J Behav Med.* 2006;29(1):17-27.
155. Osborn RL, Demoncada AC, Feuerstein M. Psychosocial interventions for depression, anxiety, and quality of life in cancer survivors: meta-analyses. *Int J Psychiatry Med.* 2006;36(1):13-34.
156. Dziak J, Collins L, Wagner A. FactorialPowerPlan SAS macro suite users' guide. In: University Park: The Methodology Center, Penn State; 2013.
157. Baker TB, Smith SS, Bolt DM, et al. Implementing Clinical Research Using Factorial Designs: A Primer. *Behav Ther.*
158. MacKinnon DP, Lockwood CM, Hoffman JM, West SG, Sheets V. A comparison of methods to test mediation and other intervening variable effects. *Psychol Methods.* 2002;7(1):83-104.
159. Aiken LS, West SG, Reno RR. *Multiple regression: testing and interpreting interactions.* Newbury Park, Calif.: Sage Publications; 1991.