Protocol paper: Multi-site, cluster-randomized clinical trial for optimizing functional outcomes of older cancer survivors after chemotherapy

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Authors' Contributions
All authors provided comments and feedback for improvement the manuscript. All authors approved the final version of the manuscript and are responsible for their contributions.

Declaration of Competing Interest
The authors declare that they have no competing interests.

Ethics Approval and Consent to Participate
This protocol (URCC19178) was approved by the NCI Central Institutional Review Board, which is acting as the single Institutional Review Board of record for all study sites. The protocol is registered at clinicaltrials.gov (NCT05006482).

Consent for Publication
Not applicable.

Appendix A. Supplementary Data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.jgo.2022.03.001.
Abstract

**Background:** Cancer survivors over the age of 65 have unique needs due to the higher prevalence of functional and cognitive impairment, comorbidities, geriatric syndromes, and greater need for social support after chemotherapy. In this study, we will evaluate whether a Geriatric Evaluation and Management-Survivorship (GEMS) intervention improves functional outcomes important to older cancer survivors following chemotherapy.

**Methods:** A cluster-randomized trial will be conducted in approximately 30 community oncology practices affiliated with the University of Rochester Cancer Center (URCC) National Cancer Institute Community Oncology Research Program (NCORP) Research Base. Participating sites will be randomized to the GEMS intervention, which includes Advanced Practice Practitioner (APP)-directed geriatric evaluation and management (GEM), and Survivorship Health Education (SHE) that is combined with Exercise for Cancer Patients (EXCAP©®), or usual care. Cancer survivors will be recruited from community oncology practices (of participating oncology physicians and APPs) after the enrolled clinicians have consented and completed a baseline survey. We will enroll 780 cancer survivors aged 65 years and older who have completed curative-intent chemotherapy for a solid tumor malignancy within four weeks of study enrollment. Cancer survivors will be asked to choose one caregiver to also participate for a total up to 780 caregivers. The primary aim is to compare the effectiveness of GEMS for improving patient-reported physical function at six months. The secondary aim is to compare effectiveness of GEMS for improving patient-reported cognitive function at six months. Tertiary aims include comparing the effectiveness of GEMS for improving: 1) Patient-reported physical function at twelve months; 2) objectively assessed physical function at six and twelve months; and 3) patient-reported cognitive function at twelve months and objectively assessed cognitive function at six and twelve months. Exploratory health care aims include: 1) Survivor satisfaction with care, 2) APP communication with primary care physicians (PCPs), 3) completion of referral appointments, and 4) hospitalizations at six and twelve months. Exploratory caregiver aims include: 1) Caregiver distress; 2) caregiver quality of life; 3) caregiver burden; and 4) satisfaction with patient care at six and twelve months.

**Discussion:** If successful, GEMS would be an option for a standardized APP-led survivorship care intervention.

**Trial Registration:** ClinicalTrials.gov NCT05006482, registered on August 9, 2021.

**Keywords**

Geriatric assessment; Geriatric evaluation; Survivorship health education; Cluster-randomized trial; Cancer survivor; Caregiver; Chemotherapy; Curative-intent; Survivorship

1. **Background**

The population of older cancer survivors is increasing. These are older patients who have completed curative-intent (i.e., adjuvant) chemotherapy for any solid tumor malignancy.
Currently, 64% of cancer survivors are aged 65 years and older; by 2040, approximately 50% will be aged 75 years and older with approximately 18% aged 85 years and older [1,2]. Older cancer survivors are at a higher risk for adverse outcomes and experience physical and cognitive impairments following curative-intent chemotherapy [3,4]. The National Cancer Institute (NCI) [5,6], American Society of Clinical Oncology (ASCO) [7,8], and the Cancer and Aging Research Group (CARG) [9,10] recommend aging-sensitive interventions for older cancer survivors and their caregivers.

The National Academy of Medicine (NAM; previously Institute of Medicine) reported that older cancer survivors have unique needs due to the higher prevalence of functional and cognitive impairment, comorbidities, geriatric syndromes, and greater need for social support following treatment [11,12]. Older patients report more interference with function from symptomatic toxicities (e.g., fatigue, pain) than younger patients and are at higher risk for unplanned hospitalizations and mortality [13]. Hence, older patients with cancer consistently place a high priority on the recovery of their physical and cognitive function after chemotherapy [14–20]. Yet, the majority of older patients with cancer are treated based on extrapolations of evidence derived from clinical trials enrolling mainly younger adults or fit older adults (e.g., those without other health status conditions). Extrapolating data on the safety and efficacy from these trials for use in vulnerable or frail older adults increases their risks for long-term complications in survivorship [21].

The ASCO guidelines recommend survivorship care plans (SCPs) for all older adult patients transitioning out of active treatment [22]. However, a recent systematic review [23] found: 1) Current SCPs do not adequately improve physical and psychosocial outcomes, 2) few studies facilitated follow-up with advanced practice practitioners (APPs) or other clinicians, 3) only two studies included a significant number of cancer survivors over age 65 [24,25], and 4) none of these studies addressed aging-related conditions through the use of specialized assessment and management of problems for older adults. Research suggests that, for SCPs to be effective, in addition to survivorship care plan summaries, cancer survivors need explicit help to implement the survivorship care plan recommendations (e.g., to schedule and attend referral appointments, modify lifestyle via health education) [26–32]. The survivorship care plans need to be individually tailored and feasible for older cancer survivors and incorporate their caregivers.

Caregivers experience distress and low satisfaction with care when the cancer survivor’s function is poor [33,34]. The NCI and experts recommend that interventions engage caregivers as partners in survivorship care [35–38]. When cancer survivors experience physical and cognitive impairment, caregivers become distressed and less satisfied with the survivors’ care because they are burdened with increased caregiver work, more responsibility to communicate with providers, and increased need to access services necessary for the cancer survivors [36,39,40].

Team-based care (by at least two clinicians), where clinicians work collaboratively with patients and caregivers to accomplish shared goals within and across settings to achieve coordinated high quality care, is recommended for the provision of health services to older adults and families [41]. As shown in Fig. 1, interventions guided by physical and/or
occupational therapists [42–48], clinical exercise physiologists [28,30,31,49,50], cognitive specialists [51–54], psychologists [55–57], and pharmacists [58–60] are associated with improved outcomes in older patients with cancer. However, a standardized approach to surveillance and management of aging-related conditions by teams is not often employed [61].

An APP is a health care provider who has completed advanced training and education that qualifies them to 1) manage medical problems and 2) prescribe and manage treatments within their scope of training. In the United States regulations, licensure and scope of practice vary based on state law and regulations. It most commonly refers to a nurse practitioner (NP) or physician assistant (PA), as well as other licensed, nonphysician providers, including certified clinical nurse specialists and certified nurse anesthetists. NPs are registered nurses with additional education and clinical training at the master’s or doctoral degree level. Nurses must complete at least 1000 h of clinical practice in a focused area, such as pediatric, adult, or geriatric medicine, to earn an NP degree. A PA, on the other hand, trains for two years—frequently alongside medical students. Physician assistant students complete at least 2000 h of supervised practice before graduation [62]. Despite differences in training and licensure, APPs in oncology clinics play an essential role in the transition period after chemotherapy by facilitating surveillance and management of symptomatic toxicities and coordination of care [63–66]. In geriatric medicine, APPs direct shared care and train other disciplines in aging [67–70]. While experts have advocated for APPs to play a key role in oncology [37,65,71], gaps remain regarding the efficacy of aging-sensitive APP-directed survivorship interventions [23].

To our knowledge, this is the first cluster randomized trial evaluating whether a standardized intervention—APP-directed Geriatric Evaluation and Management (GEM) combined with Survivorship Health Education (SHE) and Exercise for Cancer Patients (EXCAP©®)—can optimize outcomes important to older cancer survivors and their caregivers following curative-intent chemotherapy. We hypothesize that Geriatric Evaluation and Management-Survivorship (GEMS), compared to usual care, will significantly improve physical function and, secondarily, cognitive function at six months. We also hypothesize that GEMS, compared to usual care, will improve satisfaction with care, completion of referral appointments, and hospitalizations in older cancer survivors, and will improve oncology APP communication with primary care physicians (PCPs) as well as reduce distress and improve satisfaction with care in caregivers.

2. Methods

2.1. Aims, Design, and Setting

2.1.1. Aims—Our specific aims are as follows: The primary aim is to compare the effectiveness of GEMS for improving patient-reported physical function at six months. The secondary aim is to compare effectiveness of GEMS for improving patient-reported cognitive function at six months. Tertiary aims include comparing the effectiveness of GEMS for improving: 1) Patient-reported physical function at twelve months; 2) objectively assessed physical function at six and twelve months; and 3) patient-reported cognitive function at six and twelve months. Exploratory health care aims include: 1) Survivor
satisfaction with care, 2) APP communication with PCPs, 3) completion of referral appointments, and 4) hospitalizations at six and twelve months. Exploratory caregiver aims include: 1) Caregiver distress; 2) caregiver quality of life; 3) caregiver burden; and 4) satisfaction with patient care at six and twelve months.

2.1.2. Design and Setting of the Study—This clinical trial uses a cluster-randomized design and will be conducted in at least 30 community oncology practice clusters within the NCI Community Oncology Research Program (NCORP) Research Base network; the University of Rochester Cancer Center (URCC) NCORP Research Base will serve as the coordinating site.

The NCI’s Central Institutional Review Board approved the study on June 11, 2021. All participants will provide informed consent. We will enroll all groups (practice clusters, oncologists, APPs, SHE instructors, older cancer survivors, caregivers) using inclusion and exclusion criteria (Table 1, see Appendix) until the target cancer survivor enrollment number is met (See Table 2).

2.1.3. Description of Arms and Intervention—Practices will enroll, on average, 26 cancer survivors per practice cluster for a total of 780 cancer survivors and up to 780 caregivers (estimated number of caregivers is 500). A practice cluster is defined as any practice location where staff (oncology physician, APPs, coordinators) work independently and do not cross over into another practice location. Each practice cluster will be randomly assigned to the GEMS intervention arm or the usual care arm in a 1:1 ratio.

In the intervention arm, the APPs, cancer survivors, and caregivers will complete and review GA-guided management recommendations. Cancer survivors and caregivers will also participate in the SHE combined with EXCAP©® sessions. In the usual care arm, cancer survivors and caregivers will participate in routine follow-up care without restrictions at their practices. Coordinators will capture routine survivorship care practices.

2.1.4. Geriatric Evaluation and Management for Survivorship (GEMS) Intervention—This is an innovative, standardized intervention based on the ASCO guidelines [7] and expert consensus for evaluating and managing the care of older cancer survivors. GEMS intervention triages and manages the critical aging- and treatment-related medical, physical, and psychosocial issues that arise for older cancer survivors at the end of chemotherapy as they transition into long-term survivorship. The intervention engages the caregiver to foster better outcomes for both the cancer survivor and caregiver [34]. GEMS is a multi-level intervention that facilitates coordination of care between the older cancer survivor, caregiver, APPs, oncology physicians, PCPs, and other relevant clinicians to effectively address aging-related conditions and survivorship needs.

The APP-directed GEMS intervention consists of three major components: 1) geriatric assessment (GA) that evaluates the medical, physical, and psychosocial effects of treatment; 2) specific GA-guided management recommendations including referrals to relevant clinical disciplines/services; and 3) SHE program combined with an individually tailored exercise program EXCAP©® for cancer survivors and caregivers. All intervention components will
be offered in-person (or via tele-health, if it is not convenient or feasible to participate in-person).

2.1.4.1. **Geriatric Assessment (GA):** The GA measures are validated tools with established scoring thresholds, described in the Supplementary Tables 1–3 (see Appendix). Scores signifying impairment to trigger management recommendations are summarized in Table 3. The measures were selected based upon extensive data in the geriatric literature demonstrating predictive value as well as feasibility data in multiple studies of older patients with cancer as well as the ASCO guidelines. In the intervention arm, either the coordinator or the APP can administer a standardized GA to the cancer survivor, which includes patient-reported and objective measures to evaluate eight geriatric domains (Table 3).

2.1.4.2. **GA-Guided Management Recommendations:** The APPs and/or coordinators can enter cancer survivors’ test results into a password-protected portal, which automatically generates a summary that includes tailored evidence-based management recommendations and suggestions for referrals. Then, APPs will review the results with the cancer survivors and caregivers during a one-hour clinic visit in-person (or via tele-health); in collaboration with the cancer survivors and caregivers, the referrals will be prioritized and the top three scheduled. The APPs will provide the summary of the cancer survivors’ GA results and management recommendations and referrals to cancer survivors, caregivers, and PCPs. In addition, APPs will have 30-min visits in-person (or via tele-health) with cancer survivors and caregivers at three and six months to determine if referrals and SHE-EXCAP®® sessions are being completed. The APPs will triage and facilitate ongoing completion of management recommendations as needed, as well as discuss management plans with oncology physicians and PCPs and document communications in the medical chart. The cancer survivor and caregiver (if available) will meet with the APP in-person (or via tele-health) at three and six months (30 min minimum) to review the completion of referrals and provide ongoing symptom management. After each visit, the APP will send all information (including the GA summary and list of management recommendations) to the cancer survivor’s PCP and also call the primary care team to provide updates.

2.1.4.3. **Survivorship Health Education (SHE) Combined with Exercise for Cancer Patients (EXCAP®®):** Although SHE and EXCAP®® are explained individually for the purposes of detailed description of each, they will be delivered as a joint component of the GEMS intervention.

2.1.5. **SHE—** The SHE program (Table 4) is a standardized didactic and experiential component of the intervention that builds on ASCO survivorship recommendations and reinforces GEM recommendations. The SHE program consists of eight face-to-face, 75-min group sessions delivered twice a week over four weeks by a SHE instructor. All SHE participants will receive the “ASCO® Answers Cancer Survivorship” booklet in the first session. The participants will attend SHE sessions in a group setting either in-person or virtually via tele-health. Each participating NCORP practice cluster will be responsible for identifying qualified SHE instructors and medical interpreters for Spanish-speaking participants. All qualified SHE instructors will complete a one-on-one interview, go through
training, and use the provided SHE materials as a guide for delivering SHE group sessions. The third SHE session will be video-recorded to assess intervention fidelity.

2.1.6. SHE-EXCAP©®—EXCAP©® is a home-based, individually tailored exercise program combining aerobic walking and resistance band exercises. The EXCAP©® program will be introduced and individually prescribed in the third SHE session, “Exercise Behavioral Change.” During the third session, the SHE instructor will provide an EXCAP©® kit containing an EXCAP©® manual and resistance bands to SHE participants. In addition, a pedometer will be provided to participants at the first SHE session to collect daily steps for the following six days. During the third SHE session, the SHE instructor will demonstrate each resistance band exercise and provide the individually tailored walking and resistance band exercise prescriptions.

2.2. Fidelity of GEMS Intervention

Fidelity will be ensured through: 1) Review of GEM implementation for the first two enrolled cancer survivors for each APP and ongoing checks for GA scoring and 2) videotaping of the third SHE session for evaluation of content and quality. Both APPs and SHE instructors may be subject to re-training if the content and quality criteria are not met.

2.3. RE-AIM (Reach, Effectiveness, Adoption, Implementation, and Maintenance) Framework

While this is an efficacy study, hypothesis-generating data will be collected to guide the design of future effectiveness or implementation studies and efforts for scaling-up the GEMS intervention if study results are positive. Pilot data collection to inform future scalability efforts is guided by the RE-AIM [72] framework, which is used in dissemination and implementation research to enhance the quality and speed of efforts to translate research into the “real world.” In the intervention arm, APPs and coordinators will complete the online RE-AIM tool at baseline (prior to enrolling their first cancer survivor at the practice cluster), six months, and twelve months to assess implementation progress and fidelity of the implementation strategy. Responses will be discussed during separate 60-min focus groups with the staff of each of the practices randomized to the intervention arm. The focus groups will be audio-recorded for subsequent transcription and qualitative analysis.

2.4. Measures

Questionnaires for each of the aims are listed in the Tables and include information on which assessments are available in Spanish and which assessments will be administered/translated using medical interpreters for Spanish-speaking cancer survivors and caregivers.

2.4.1. Cancer Survivor and Caregiver Questionnaires—Cancer survivors will complete questionnaires at run-in/baseline, three months, six months, and twelve months. Caregivers will complete questionnaires at the same time points as cancer survivors. Cancer survivors and caregivers (if available) will be asked to complete questionnaires at home, in-person, or via tele-health (for those that can be completed virtually). All questionnaires can be mailed to be completed at home prior to in-person visit.
2.4.2. **APP and Oncology Physician Questionnaires**—Advanced practice practitioners and oncology physicians will complete a baseline Research Electronic Data Capture (REDCap) questionnaire prior to their first cancer survivor consenting to the study. This questionnaire will provide a study overview, confirm acknowledgment of participation, and capture demographics, comfort with geriatrics, and survivorship care practices. The APPs and oncology physicians will also complete a brief follow-up questionnaire at the end of the study.

2.4.3. **Chart Abstraction and Claims**—All clinic visit notes from the APP visit, summary notes sent to APPs and PCPs, referral visit notes, phone call information between site staff and cancer survivors or site staff and PCPs, medical records, emergency room/hospitalization visit notes and discharge summaries, and all APP communication with PCPs and other providers will be requested to validate the collected data. If there is missing information or conflicting medical information from the questionnaires, we will also obtain medical records in order to verify information about disease location, pathology, and stage from charts.

2.5. **Study Procedures**

2.5.1. **Practice-Based Phase**—The URCC NCORP Research Base staff will review completed Practice Cluster Interest Forms and interview interested staff to confirm practice eligibility. Once the practice cluster has been approved by the URCC NCORP Research Base to participate, APPs and oncology physicians will complete a questionnaire that provides an overview of the study and captures information on demographics and Comfort with Survivorship Care Practices for Older Adults. Once at least one APP is enrolled and coordinators complete training, the practice cluster will be randomized. If assigned to the intervention arm, the practice cluster’s personnel (APP, coordinator) will receive training on the intervention prior to enrolling their first cancer survivor.

2.5.2. **Patient-Based Phase: Cancer Survivor (and Caregiver if Available)**—Coordinators, with oversight from the oncology team, can screen for patients aged 65 and older who are either currently receiving or have recently completed curative-intent (i.e., adjuvant) chemotherapy for any solid tumor malignancy. Eligible cancer survivors will undergo informed consent (in-person or via tele-health). Run-in study procedures can occur during the last four weeks of adjuvant chemotherapy but no later than four weeks after the completion of adjuvant chemotherapy. After the cancer survivor has consented, the first assessment that the coordinator will administer is the Blessed-Orientation-Memory-Concentration test (BOMC) [73]; cancer survivors with a BOMC score of ≥11 will not move forward with study procedures. Cancer survivors with BOMC score of <11 can continue participation and can identify one caregiver to participate; cancer survivors without an available caregiver are still eligible if approved by URCC NCORP. The coordinator will enroll the eligible cancer survivor and caregiver and provide them the patient-reported assessments to complete; all can be completed via tele-health or in-person. The cancer survivor’s patient-reported assessments should be completed prior to baseline registration. At the baseline visit, coordinator-administered assessments will be completed for the cancer survivor and caregiver. The Six Minute Walk Test (6MWT) [74,75] and Trail Making Tests...
(TMT A/B) [76] will be completed in-person, while the Mini-Cog [77–79], Short Physical Performance Battery (SPPB) [80,81], and Controlled Oral Word Association (COWA) [82–84] can be completed via tele-health or in-person. If assessments that require in-person data collection are unable to be completed due to COVID-19, other health-related concerns, or personal factors, they will be documented as missing.

In the GEMS intervention arm, APPs will deliver GEM. The APPs and/or coordinators will provide cancer survivors with the GA forms to be completed during run-in/baseline and will schedule a clinic visit (baseline, one hour minimum) to occur in-person to be conducted within four weeks of completing chemotherapy. At the baseline visit, APPs will complete and score the GA and enter the scores into a password-protected web portal to create a tailored summary and list of management recommendations, including referrals to relevant clinicians. The APP will review this information with the cancer survivor and their caregiver in conjunction with a review of the medical and treatment history. The APP will review the recommendations for GA impairments, symptom management, and health education. In collaboration with the cancer survivor and caregiver, the APP will triage the referrals so the top three referrals will be completed first; referrals will be prioritized by the APP through discussions with the cancer survivor and caregiver. The APP will oversee scheduling of all referrals, including the SHE and EXCAP sessions, and will discuss a care plan with the oncology physician and ensure that appropriate clinical documentation is completed and disseminated. All intervention components, including all SHE sessions, will be completed by the six-month assessment. To collect data to inform future scalability efforts, the URCC NCORP Research Base team will conduct focus groups with staff in the intervention arm at baseline, six, and twelve months.

In the usual care arm, cancer survivors and caregivers will continue to receive routine survivorship follow-up care at their practices. Cancer survivors will complete GA in-person (or via tele-health) during run-in/baseline, but no GA summary score or list of management recommendations will be provided to the oncology teams to review with the cancer survivor and their caregivers. We will however, provide information regarding clinically significant depression (i.e., score of ≥11 on the Geriatric Depression Scale [GDS] [85] via completing the Physician Notification of the Depression Symptoms Form).

In both arms, cancer survivors and caregivers will complete assessments at three, six, and twelve months in-person (or via tele-health). The coordinators will collect information about APP communication with PCPs, the number and completion of referrals, and healthcare utilization (e.g., emergency department visits and hospitalizations).

2.6. Statistical Analysis

2.6.1. Primary Outcome—The primary outcome will be the change in patient-reported physical function as assessed by Physical Well-Being (PWB) [86–88] subscale score of Functional Assessment of Chronic Illness-Fatigue (FACIT-F) scale as measured from baseline to six months. The primary aim of this study will test the efficacy of the GEMS intervention on self-reported physical function at six months (primary outcome) by calculating the average between-arm difference in change in the FACIT-PWB subscale score from baseline to six months.
2.6.2. Sample Size—We plan to enroll at least 30 practices (15 per arm) with a minimum of 10 and maximum of 40 cancer survivors per practice. For the sample size and power calculation, we consider a within-patient correlation of $\rho = 0.50$ between baseline and the six-month assessment of PWB. We assume an intra-cluster correlation coefficient (ICC) of 0.05, indicating the influence of practice cluster on FACIT-PWB. Under these model assumptions, the minimum detectable between arms difference ($\Delta$) can be estimated as

$$\Delta = \left( Z_{1 - \alpha/2} + Z_{1 - \beta} \right) \sqrt{\frac{2 \times DE \times (1 - \rho^2) \times \sigma^2}{N}},$$

where $N$ is number of cancer survivors per arm; $\alpha$ and $\beta$ are type I and II error rates; $DE$ corresponds to the design effect penalty due to randomization of clusters, $DE = 1 + (k-1) \times ICC$, where $k$ is the number of cancer survivors per cluster; and $(1-\rho^2) \times \sigma^2$ corresponds to the analysis of covariance (ANCOVA) adjustment to variance due to the within-patient pre-post correlation $\rho$ of the outcome measure. Given the above assumptions, a sample of 600 evaluable cancer survivors ($N = 300$ per arm, 20 per practice) will provide 86% power at the two-sided significance level ($\alpha$) of 0.05 to detect an effect size (standardized $\sigma^2 = 1$) mean between arm difference of 0.30. To account for the potential drop-out based on previous studies (approximately 23%) [89]; we plan to enroll 780 cancer survivors (26 per practice).

2.6.3. Statistical Analysis for Aims—To estimate the intervention effects, we will use an ANCOVA model with an additional random effect term to account for clustering. The model will include PWB at six months as the outcome and study arm, baseline value of PWB, and rural vs. non-rural practice cluster (stratification factor in randomization) as fixed effects. Practice cluster will be included as a random effect. Estimation will be performed using the restricted maximum likelihood (REML) method, and fixed effects inferences will be performed using an F-test. To compare long-term effects of the intervention on PWB at twelve months we will use a longitudinal linear mixed model (LMM). The model outcome (dependent variable) will be PWB with measures repeated at three, six, and twelve-month assessments. We will apply the same analytical approach as for the primary aim to assess the intervention effect on other patient-reported outcome measures, for example perceived cognitive impairment measured using the Functional Assessment of Cancer Therapy-Cognitive Function (FACT-COG) questionnaire, Perceived Cognitive Impairment subscale (secondary outcome). To compare the effect of the GEMS intervention vs. usual care arm on survivor care satisfaction, APP communication with PCPs, cancer survivor completion of referral appointments, and health care utilization, we will use LMM for continuous outcomes or generalized LMMs (GLMM) for binary outcome measures. For all models we will evaluate goodness of fit and, if necessary, apply a transformation. To explore the efficacy of the GEMS intervention for improving caregiver distress and care satisfaction and communication, caregiver quality of life and caregiver burden, we will follow a similar statistical plan. In addition, we will collect hypothesis-generating data to inform future scalability efforts. Open-ended questions on the participant feedback forms and the RE-AIM tool, and audio-recorded interviews will be transcribed and coded by study team members, using a qualitative content analysis approach to interpret the content of text data through the systematic classification process of coding and identifying themes or patterns.
3. Discussion

A growing population of older cancer survivors are at a higher risk for poor functional outcomes following curative-intent chemotherapy, and current survivorship care plans are not tailored to address the unique needs and health disparities among older cancer survivors and their caregivers [23]. Using large data sets, we have shown that curative-intent chemotherapy leads to a high prevalence of toxicity in older patients [89]. GA-identified impairments in domains including function, nutrition, comorbidity, mental health, and cognition are associated with increased hospitalizations and mortality, suggesting the need for better management. Studies of GA-guided management recommendations in older patients with cancer demonstrate a trend toward improved function and more appropriate healthcare utilization [90]. Our APP-directed GEMS intervention provides an opportunity to go beyond routine survivorship care plans to improve physical and cognitive function, increase satisfaction of care, and reduce hospitalizations, and may be efficacious for improving outcomes important to older cancer survivors and caregivers.

While studies have shown GEM is valued by oncologists [61,90], without leadership from APPs, adherence to management recommendations is not optimal [91–94]. Research shows that providing older adults with survivorship care plan summaries does not improve functional outcomes [95]; older patients need additional help from APPs to implement aging-sensitive referrals and services (Fig. 1) as part of their transition to long-term survivorship. Using expert consensus and guidelines [96,97], we developed and tested the GEM intervention with community oncology practices in two large trials (URCC 13070, “Communicating about Aging and Cancer Health” or “COACH” and URCC 13059, “Geriatric Assessment for Patients 70+” or “GAP”), demonstrating feasibility and benefits for older patients with cancer and their caregivers [89]. In COACH [89], among 541 eligible patients (mean age 77; 48.8% female) and 414 caregivers (mean age 67; 74.9% female), we showed that there were more aging-related conversations in the intervention arm (difference 3.59 conversations, \( p < 0.001 \)), and more conversations were higher quality and led to higher number of recommendations. On average, there were four GA-guided referrals per patient (range 0–6). In COACH [89], aging-related conditions and symptom burden independently explained variance in FACIT-PWB [98–100]. Also, older patients reported that their preference would be to forego survival benefits if treatment would impair function (42%) or memory (57%) [89].

ASCO recommends that cancer survivors receive comprehensive information regarding their diagnosis, treatments, and health education [22]. The Cancer and Aging Research Group provided information related to COVID-19 and cancer care delivery for older patients with cancer [101]. Based on the existing data, it is clear that older adults with cancer, especially those with comorbidities and perhaps those who have had recent treatment, are at much higher risk for adverse outcomes (including hospitalization, intubation, intensive care unit admission, and death). During COVID-19, we optimized our ability to conduct GEM through tele-health using a team-based approach [102].

These data suggest that older cancer survivors have a high prevalence of aging-related impairments and physical and functional decline, which persist into long-term survivorship.
after curative-intent chemotherapy. Caregivers experience distress and dissatisfaction with
care when older patients with cancer have functional impairments [34]. We hypothesize that
our APP-directed GEMS intervention will be beneficial for improving outcomes important
to older cancer survivors and caregivers. Hence, with this study, we will evaluate whether
providing the GEMS intervention to older cancer survivors (within four weeks of completing
curative-intent chemotherapy) and their caregivers can improve the physical and cognitive
functions of cancer survivors, when compared to usual care. We hypothesize that providing
a multidimensional, interdisciplinary, aging-sensitive survivorship care intervention focused
on triaging and managing an older cancer survivor’s medical, physical, and psychosocial
need will optimize outcomes for older cancer survivors and their caregivers during the
period immediately following chemotherapy.

3.1. Strengths and Potential Limitations

There are number of strengths to this study. This is one of the few studies [89] that
includes older cancer survivors aged 65 years and older and the first study to address the
unique needs and health disparities among older cancer survivors (especially those aged
75 years and older). We combined our two previously successful interventions, GEM and
SHE-EXCAP© to create GEMS, and herein will test its efficacy to improve physical
and cognitive functions among older cancer survivors. Second, we include caregivers as
study participants. Over 60% of the individuals caring for older cancer survivors are
older themselves and have a high prevalence of their own comorbid conditions. Caregivers
experience additional distress and low satisfaction with care when the cancer survivor’s
function is poor [34]. The NCI and other experts recommend that survivorship interventions
should be tailored and feasible not only for older cancer survivors, but also should engage
their caregivers as partners in survivorship care [35–38]. In addition, this is the first study to
challenge the current survivorship care paradigm by using an APP-directed intervention to
guide team-based care with other clinicians and engage caregivers. Last, but not least, this
study will be conducted in community practices (including those that are rural), where the
majority of older adults receive care, as opposed to academic medical centers, and therefore
the results will be generalizable to the majority of older American adults.

While this study uses an innovative approach to create aging-sensitive “personalized
pathways” for survivorship care that is tailored for two vulnerable groups—older cancer
survivors and their caregivers—there are several limitations worth noting. Potential
limitations include limited generalizability as we are aiming to enroll a specific population
of older cancer survivors who are commonly seen in community oncology practices and are
underrepresented in research studies. In addition, there is a risk of selection bias inherent
in cluster randomization. Oncologists and APPs in both intervention arms (GEMS vs. usual
care) are not blinded to the study conditions, and simply being part of the study may lead to
increased incorporation of GA recommendations and discussion of aging-related concerns in
both arms.
4. Conclusion

The results of this study will be used to determine the efficacy of GEMS intervention for improving physical and cognitive function among older cancer survivors and their caregivers. If the intervention is shown to be effective, it may lead to increased use of GEMS as a standardized survivorship care intervention, promoting the identification and management of aging-related concerns that are not captured by routine oncology assessments, and lead to improved functional outcomes and more appropriate healthcare utilization among older cancer survivors, especially those aged 65 years and older.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Availability of Data and Materials

The investigators will provide access to data according to NIH and URCC NCORP policies.

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Fig. 1.
APP-directed management for older cancer survivors.
Fig. 2.
Study schema.

Note: NCORP = National Cancer Institute Community Oncology Research Program; GEMS = Geriatric Evaluation and Management combined with Survivorship Health Education and Exercise for Cancer Patients (EXCAP©®); APP = Advanced Practice Practitioner; FACIT-PWB = Functional Assessment of Chronic Illness Therapy – Fatigue Physical Well-being Subscale; TMT A/B = Trail Making Part A and Part B; COWA = Controlled Oral Word Association (i.e., FAS Test); PCP = Primary Care Physician; ED = Emergency Department.
| Inclusion Criteria | Exclusion Criteria |
|-------------------|-------------------|
| **Practice Cluster** | ■ Identify one (or more) advanced practice practitioner (APP). |
| | ■ Desire to participate in the study, including presence of an investigator (e.g., NCORP PI, oncology physician, APP) and/or program administrator/supervisor who is willing to be a key contact. |
| | ■ Agreement that enrolled cancer survivors and caregivers (if available) will not formally be offered other survivorship plans or programs and that a Survivorship Health Education instructor(s) will be identified for your practice cluster. |
| | ■ Demonstrated support/buy-in from oncology physicians and APPs who are willing to enroll cancer survivors. |
| | ■ Agreement of practice leadership and staff (e.g., study coordinator) to support study activities. |
| | ■ If necessary, willingness to participate in a phone interview to determine capacity to implement the intervention. |
| **Oncology Physician and APP** | ■ Works at a URCC NCORP practice with no plans to leave that practice or retire within two years of enrollment into the study. |
| **SHE Instructors** | ■ Has experience in oncology and/or geriatrics (APP). |
| | ■ Has license to practice (APP). |
| | ■ Must have a minimum of a Bachelor’s degree in a health-related field (e.g., exercise science/kinesiology, health education, public health, nursing, psychology, social work, other). |
| | ■ The SHE instructor is also required to have a professional fitness certification to perform exercise prescription and instruction (individual and/or group) via the American College of Sports Medicine (ACSM) or similar fitness certification organizations (e.g., American Council on Exercise, National Council on Strength and Fitness, National Strength and Conditioning Association, YMCA). ACSM Cancer Exercise Trainer certification is preferred, but not required. |
| | ■ SHE instructors must also have ≥2 years of experience working with individuals who are cancer patients or survivors, or individuals with other chronic diseases or disabilities. It is strongly preferred that SHE instructors have experience working with older individuals. |
| | ■ SHE instructor experience is required in the areas of teaching healthy lifestyle behaviors, prescribing individualized exercise, and/or teaching group exercise classes. |
| **Cancer Survivor** | ■ Have surgery planned within six months of informed consent. Cancer survivors who previously had surgery are eligible. |
| | ■ Have a condition that precludes their ability to participate in informed consent or procedures (e.g., dementia and/or Blessed Orientation Memory Concentration (BOMC) Score ≥11). |
| | ■ Caregivers unable to understand the informed consent form or study procedures due to cognitive, health, or sensory impairment will be excluded. |
| | ■ Capacity to conduct informed consent procedures and study procedures will be determined by the coordinators in collaboration with the cancer survivors’ oncologists. |
| | ■ Have surgery planned within six months of informed consent. Caregivers who previously had surgery are eligible. |
| **Caregiver** | ■ 65 years of age or older. |
| | ■ Have completed or will have completed curative-intent adjuvant chemotherapy for any solid tumor malignancy in last 4 weeks. |
| | ■ Be willing and able to come in for study visits or willing to undergo informed consent and assessments remotely via tele-health visits when necessary. |
| | ■ Be willing and able to provide informed consent and must sign consent in-person or remotely if it is not convenient or feasible to provide informed consent in-person. |
| | ■ Speak and read English and/or Spanish. Spanish-speaking cancer survivors are eligible as long as there are appropriate resources in place for completion of study procedures at the practice site. |
| | ■ 18 years of age or older. |
| | ■ Selected by the cancer survivor when asked if there is a “family member, partner, friend or caregiver [age 18 years or older] with whom you discuss or who can be helpful in health-related matters.” A caregiver need not be someone who lives with the cancer survivor or provides direct hands-on care. |
| | ■ Speak and read English and/or Spanish. Spanish-speaking caregivers are eligible as long as there are appropriate resources in place for completion of study procedures. |
### Table 2

#### Outcome Measures

(Measures will be collected at run-in, baseline, 3, 6, and/or 12 months).

| Outcome | Measures | Descriptions | References |
|---------|----------|--------------|------------|
| Primary | Functional Assessment of Chronic Illness Therapy-Fatigue (FACT-F) - Physical Well-being Subscale (FACT-PWB) | The FACT-F is a 40-item questionnaire divided into five domains: Physical well-being (PWB; 7-items), social/family well-being (SWB; 7-items), emotional well-being (EWB; 6-items), functional well-being (FWB; 7-items), and fatigue (15-items). Each question uses a 5-point rating scale (0 = Not at all; 1 = A little bit; 2 = Some what; 3 = Quite a bit; 4 = Very much). The FACT-F has been validated in the geriatric population. It has consistently demonstrated high internal validity and high test-retest reliability. The FACT-PWB is used for assessing primary survivor aim to capture patient-reported physical function in this study. The FACT-F will be offered both in-person and via tele-health when it is not convenient or feasible to do so in-person. | - Cella D, Lai JS, Stone A. Self-reported fatigue: one dimension or more? Lessons from the Functional Assessment of Chronic Illness Therapy–Fatigue (FACT-F) questionnaire. Support Care Cancer. 2011;19(9):1441–1450. |
| Secondary and Tertiary | FACT-Cognitive Function (FACT-Cog, version 3) | The FACT-Cog provides an overall score and subdomain scores (perceived impairment, perceived abilities, comments from others, impact on quality of life). The FACT-Cog will be offered both in-person and via tele-health when it is not convenient or feasible to do so in-person. | - van Dam FS, Schagen SB, Muller MJ, et al. Impairment of cognitive function in women receiving adjuvant treatment for high-risk breast cancer: high-dose versus standard-dose chemotherapy. J Natl Cancer Inst. 1998;90(3):210–218. |
|         | Six-Minute Walk Test (6MWT) | A validated protocol is used to derive the total distance walked in 6 min. The coordinator will administer in-person 6MWT. | - Vardy J, Wong K, Yi QL, et al. Assessing cognitive function in cancer patients. Support Care Cancer. 2006;14(11):1111–1118. |
|         | Trail Making Part A/B (TMT A/B) and Controlled Oral Word Association (COWA) (i.e., FAS test) | Trail Making (TMT) A/B is validated in English and is used to assess attention, visual scanning, psychomotor speed, and executive function. In part A, participants draw a line connected to each encircled number in sequential order. Time to complete the test (in seconds) is recorded for both parts A and B. Part A is stopped after 3 min and Part B is stopped after 5 min. It will be offered only in-person. Controlled Oral Word Association (COWA) Test (i.e., FAS Test) is validated in English and is used to assess verbal associative fluency and executive function. The test assesses fluency with naming words with F, A, and S. Participants are asked to tell the administrator as many words as possible beginning with the letter F, excluding proper nouns, and the same word with a different suffix. The participant has 60 s to list as many words as possible. The number of correct words, incorrect words, and the number of repeats if repeats will be recorded. This test takes less than 5 min to administer. Trials are repeated for the letters A and S. This will be offered both in-person and via tele-health. | - Jehn M, Halle M, Schuster T, et al. The 6-min walk test in heart failure: is it a max or sub-maximum exercise test? Eur J Appl Physiol. 2006;107(3):317–323. |
| Exploratory Health Care Outcomes | Health Care Climate Questionnaire (HCCQ) and HCCQ-Communication | This questionnaire measures patient-centered autonomy-supportive physician behaviors such as whether the patient and caregiver feel that the physician understands his/her perspective, provides choices and options, and encourages participation in decisions. The measure has been studied and validated in older patients. Similar to other studies that adapt satisfaction | - Elkin EB, Kim SH, Casper ES, Kissane DW, Schrag D. Desire for information and involvement in treatment decisions: elderly cancer patients’ preferences and their physicians’ perceptions. J Clin Oncol. 2007;25(33):5275–5280. |

- Cella D, Wilson H, Shalhoub H, et al. Content validity and psychometric evaluation of Functional Assessment of Chronic Illness Therapy–Fatigue in patients with psoriatic arthritis. J Patient Rep Outcomes. 2019;3(1):5.
| Outcome | Measures | Descriptions | References |
|---------|----------|--------------|------------|
| Health Care Utilization (Emergency Department visits, hospitalizations, and routine survivorship care practices) | | | Epstein RM, Street RL Jr. Shared mind: communication, decision making, and autonomy in serious illness. *Ann Fam Med.* 2011;9(5):454-461. |
| Participant Feedback Questionnaire | | | - Arora NK, Weaver KE, Clayman ML, Oakley-Girvan I, Potosky AL. Physicians' decision-making style and psychosocial outcomes among cancer survivors. Patient Educ Couns. 2009;77(3):404-412. |
| APP Communication with PCPs | | | - Epstein RM, Duberstein PR, Fenton JJ, et al. Effect of a Patient-Centered Communication Intervention on Oncologist-Patient Communication, Quality of Life, and Health Care Utilization in Advanced Cancer: The VOICE Randomized Clinical Trial. *JAMA Oncol.* 2017;3(1):92-100. |
| Completion of Referral Appointments | | | - Epstein RM, Street RL Jr. Shared mind: communication, decision making, and autonomy in serious illness. *Ann Fam Med.* 2011;9(5):454-461. |
| Exploratory Caregiver Outcomes | Health Care Climate Questionnaire (HCCQ) caregiver-Communication (caregiver) | This questionnaire measures provider behavior such as whether the provider answers questions and encourages caregiver participation in decisions involving the cancer survivors. The HCCQ (both original and modified for communication) is available only in English. It is offered both in-person and via tele-health. | - Elkin EB, Kim SH, Casper ES, Kissane DW, Schrag D. Desire for information and involvement in treatment decisions: elderly cancer patients' preferences and their physicians' perceptions. *J Clin Oncol.* 2007;25(33):5275-5280. |
| Distress Thermometer | This measure is widely used by health professionals to assess the level of patient and caregiver distress (on a 0-10 scale). The Distress Thermometer is translated from English to Spanish using consensus translation by a team of certified Spanish-speaking translators. It will be offered both in-person and via tele-health. | | - Fujinami R, Sun V, Zachariah F, Uman G, Grant M, Ferrell |
| Outcome | Measures | Descriptions |
|---------|----------|--------------|

References

B. Family caregivers’ distress levels related to quality of life, burden, and preparedness. *Psychooncology* 2015;24(1):54-62.
## Table 3

Geriatric assessment scores and management recommendation examples.

| Domain                  | Tool                                               | Score Signifying Impairment                                                                 | Management Recommendation Examples                                                                                   |
|-------------------------|----------------------------------------------------|-------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------|
| Functional Status       | ■ Activities of Daily Living (ADL)*                | ■ AnyADL deficit                                                                        | ■ Referral to physical/occupational therapy                                                                        |
|                         | ■ Instrumental ADLs(IADL)*                         | ■ AnyIADL deficit                                                                        | ■ Home safety evaluation                                                                                         |
|                         |                                                    | ■ Referral to physical/occupational therapy                                                | ■ Physical activity/exercise prescription                                                                        |
|                         |                                                    | ■ Home safety evaluation                                                                    |                                                                                                                 |
|                         |                                                    | ■ Education and/or handouts for fall prevention                                            |                                                                                                                 |
| Objective Physical       | ■ Short Physical Performance History*              | ■ ≤9 points                                                                               | ■ Direct communication with the primary care physician (PCP) in relation to risk of falls                       |
| Performance             | ■ Fall History*                                    | ■ Any history of falls                                                                     | ■ Referral to physical/occupational therapy                                                                       |
|                         | ■ Older Adult Resources and Services (OARS)       | ■ A lot of difficulty with any task                                                        | ■ Home safety evaluation                                                                                         |
|                         | Physical Health*                                   |                                                                                            | ■ Education and/or handouts for fall prevention                                                                    |
| Comorbidity             | ■ OARS Comorbidity*                                | ■ Patient answered “yes” to ≥3 chronic illnesses and/or one illness that interferes “a great deal” with quality of life | ■ Direct communication with PCP to develop management plan for comorbidities                                       |
|                         |                                                    |                                                                                            | ■ Communicate with relevant subspecialists (e.g., cardiologist)                                                  |
|                         |                                                    |                                                                                            | ■ Smoking cessation counselling if smoking                                                                         |
| Nutrition               | ■ Body Mass Index                                  | ■ ≤21 kg/m²                                                                               | ■ Referral to nutritionist/dietitian                                                                             |
|                         | ■ Mini Nutritional Status*                         | ■ ≤11 points                                                                               | ■ Referral to meal support services                                                                             |
|                         | ■ Weight loss                                      | ■ >10% in the last 6 months                                                                | ■ Education on a healthy diet                                                                                   |
|                         |                                                    |                                                                                            | ■ Referral for oral or swallowing assessment and intervention if appropriate                                       |
| Social Support          | ■ OARS Medical Social Support*                     | ■ Patient answers one of the social support questions indicating less than adequate support for care | ■ Referral to social worker or visiting nurse service                                                           |
|                         |                                                    |                                                                                            | ■ Financial counselling                                                                                           |
|                         |                                                    |                                                                                            | ■ Assess for elder abuse                                                                                         |
|                         |                                                    |                                                                                            | ■ Confirm health care proxy                                                                                      |
| Polypharmacy            | ■ Polypharmacy                                     | ■ ≥5 regularly scheduled prescription medications                                          | ■ Direct communication with PCP to reduce complexity of meds                                                     |
|                         |                                                    |                                                                                            | ■ Medication review of pill bottles and boxes and assessment of adherence                                         |
| Psychological Status    | ■ Generalized Anxiety Disorder (GAD)-7*            | ■ ≥10 points                                                                               | ■ Direct communication with PCP                                                                                    |
|                         | ■ Geriatric Depression Scale*                      | ■ ≥5 points                                                                               | ■ Assess for substance abuse                                                                                     |
|                         |                                                    |                                                                                            | ■ Referral to counselling or social worker                                                                         |
|                         |                                                    |                                                                                            | ■ Referral for group support options                                                                            |
| Cognition               | ■ Blessed Orientation Memory Concentration (BOMC)  | ■ ≥11                                                                                     | ■ Direct communication with PCP about cognition concerns                                                          |
|                         | ■ Mini-Cog*                                        | ■ 0 words recalled OR 1–2 words recalled + abnormal clock drawing test                     | ■ Evaluate for concurrent mood disorder                                                                          |
|                         |                                                    |                                                                                            | ■ Identify reversible causes of cognitive impairment                                                              |
|                         |                                                    |                                                                                            | ■ Referral to clinician with experience in assessing and treating cognitive impairment (e.g., neuropsychologist)    |
| General (for all)       |                                                    |                                                                                            | ■ Health care proxy information                                                                                  |
|                         |                                                    |                                                                                            | ■ Advanced care planning                                                                                        |
|                         |                                                    |                                                                                            | ■ Assessment of literacy                                                                                        |

Abbreviations: ADL (Activities of Daily Living); BOMC (Blessed-Orientation Memory Concentration Test); GAD (Generalized Anxiety Disorder); GDS (Geriatric Depression Scale); IADL (Instrumental Activities of Daily Living).
| Week | Session | Topic                                | Examples of Content Reviewed                                      |
|------|---------|--------------------------------------|-------------------------------------------------------------------|
| 1    | 1       | Cancer Survivorship Overview         | Defining Survivorship, Health records and individualized care     |
|      |         |                                      |                                                                   |
| 2    | 2       | Managing Side Effects                | Late and long-term side effects and resources                     |
|      |         |                                      |                                                                   |
| 2    | 3       | Exercise Behavior Change             | Physical Activity and Exercise: Exercise for Cancer Patients (EXCAP®) Program |
|      |         |                                      |                                                                   |
| 3    | 4       | Cancer Rehabilitation                | Concerns and challenges, counselling services, rehabilitation      |
|      |         |                                      |                                                                   |
| 6    | 5       | A Healthy Lifestyle                  | Tobacco cessation, reducing alcohol intake, nutrition              |
|      |         |                                      |                                                                   |
| 4    | 7       | Stress Management and Changes in Relationships | Reducing stress, emotional well-being support, changes in families and relationships |
|      |         |                                      |                                                                   |
| 8    | 8       | Support Groups and Resources         | Survivorship services and support                                 |
|      |         |                                      |                                                                   |
| 8    | 9       | Financial Management                 | Managing finances, organizing bills                                |