Navigation Intervention for Adolescent and Young Adult Cancer Survivors *

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Principal Investigator*: Erin E. Hahn, PhD, MPH

Sponsor: Kaiser Permanente Southern California, Department of Research and Evaluation

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Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale
Not applicable; this is the first version of the protocol		

CONFIDENTIALITY STATEMENT

This document is confidential communication. Acceptance of this document constitutes agreement by the recipient that no unpublished information contained herein will be published or disclosed without prior approval of the Principal Investigator or other participating study leadership and as consistent with the NIH terms of award.

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STATEMENT OF COMPLIANCE

(1) [The trial will be carried out in accordance with International Council on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812).

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form(s) must be obtained before any participant is consented. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form(s) will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.]

INVESTIGATOR'S SIGNATURE

The signature below constitutes the approval of this protocol and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines, as described in the *Statement of Compliance* above.

Principal Investigator or Clinical Site Investigator:

Signed:  Date: 01/29/2026

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Adaptation and Implementation of an Evidence-Based Patient Navigation Intervention for Adolescent and Young Adult Cancer Survivors
Grant Number:	1UG3CA297705-01A1
Study Description:	We propose to: 1) Adapt an evidence-based cancer-focused patient navigation program to the AYA survivor population; and 2) Plan and conduct a pragmatic stepped wedge hybrid type 2 effectiveness-implementation trial of this program within Kaiser Permanente Southern California. **PLEASE NOTE: This study is awarded in two phases. The UG3 phase has been awarded for the first two years; upon successful completion of this phase by meeting pre-defined milestones, the National Cancer Institute will provide funding for the second phase of the study (Years 3-6), which will allow our team to conduct a pragmatic stepped wedge hybrid 2 effectiveness-implementation trial of the patient navigation intervention**. Here we are focused on the initial UG3 phase and will update the protocol for the UH3 trial upon successful completion of the UG3 milestones and receipt of the UH3 award.
Objectives*:	Primary Objectives (UG3): The primary objectives in the UG3 phase of the study are to adapt and tailor an existing patient navigation program to meet the needs of AYA cancer survivors and the local clinical context via (a) qualitative research involving key stakeholders (patients, clinicians, administrators) and (b) guidance from our AYA Primary Care Survivorship Council. We will conduct a prospective, single-arm pilot study of the adapted navigation program and refine the program to enhance acceptability to patients and clinicians, enhance feasibility and effectiveness, and develop and pilot pragmatic trial evaluation tools and methods prior to the start of the UH3 phase of the trial, which will be a pragmatic stepped wedge prospective trial. Objectives will be updated for the UH3 phase once awarded. Secondary Objectives: N/A

Endpoints*:	Primary Endpoints: For the pilot test of the patient navigation program contained in the UG3 phase, we will survey patient and clinician participants. Patient survey outcomes will include patient self-efficacy, measures of care coordination and communication, barriers to care, and appropriateness and acceptability of the program. Clinician outcomes include integration of the navigation program as well as the appropriateness, acceptability, and feasibility of implementation of the program. The primary outcomes for the UH3 phase will be incorporated once awarded. Secondary Endpoints: N/A
Study Population:	Patients: In the UG3 focus groups and pilot study of the navigation intervention, we will include patients of current age of 21-45 years who received a diagnosis of breast, ovarian, cervical, testicular, colon/rectal, melanoma, endometrial, sarcoma, or thyroid cancer. Patients in the focus groups may have diagnosis years between 2019-2022, while those in the pilot test of the navigation intervention will be up to 36 months post-diagnosis. Exclusion criteria: patients with a history of leukemia or lymphoma; patients with metastatic disease at diagnosis; and patients with less than 120 days of Kaiser Permanente Southern California (KPSC) insurance membership after diagnosis of primary cancer. Clinicians and Administrators: Physicians selected to participate in focus groups or survey must be Board Certified in Internal or Family Medicine, hold a valid and current MD and be employed by the Southern California Permanente Medical Group. Nurses or Advanced Care Practitioners must hold a valid license and be employed by KPSC. Department Administrators must be employed by KPSC.
Phase* or Stage:	Other
Description of Sites/Facilities Enrolling Participants:	The UG3 phase will be conducted in a community-based integrated healthcare system, KPSC.

Description of Study Intervention/Experimental Manipulation:

In the UG3 phase, we will be adapting a patient navigation intervention to suit adolescent and young adult cancer survivors and conducting a single-site pilot test of the adapted intervention. In the UH3 phase, we will conduct a pragmatic stepped wedge hybrid effectiveness implementation trial evaluating (1) clinical effectiveness and (2) implementation outcomes, across a range of data sources.

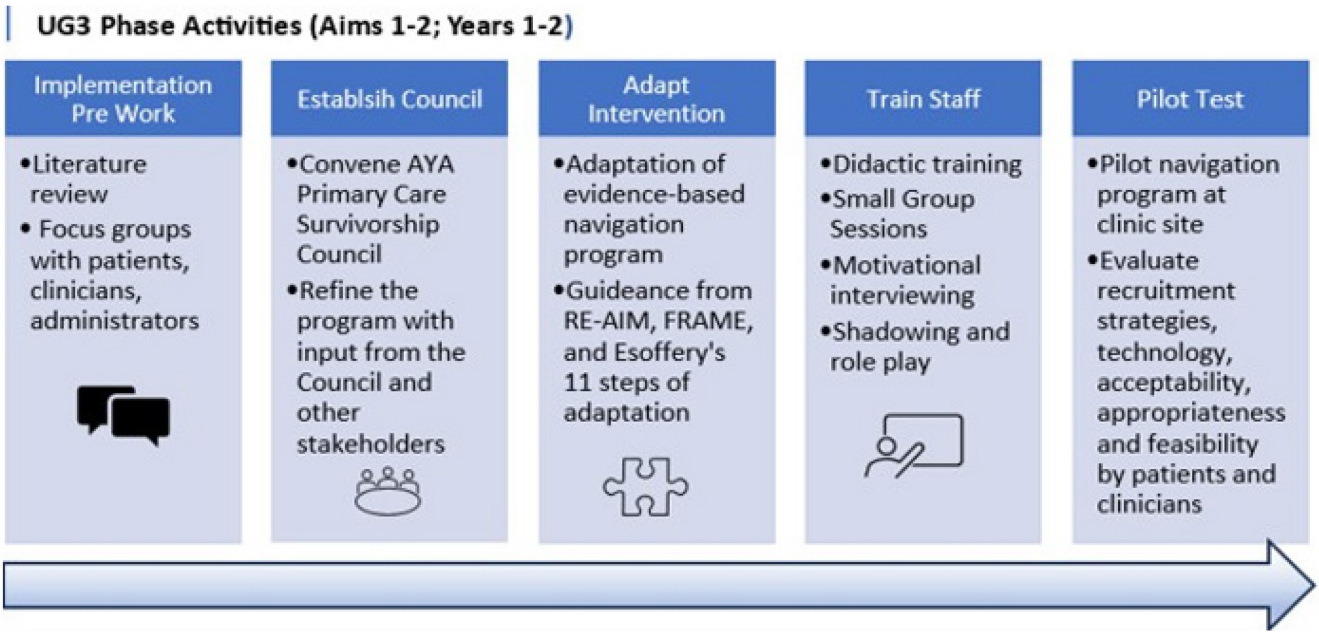
Intervention:

Navigator-level: For the pilot test in the UG3 phase, we will provide navigation training for the adapted AYA patient navigation (PN) program to at least one navigator. We anticipate that navigators will undergo a comprehensive training curriculum that draws on existing KPSC PN program trainings (e.g., KP Motivational Interviewing for Clinicians, KPSC Panel Management) and includes primary care and cancer survivorship/surveillance components and established recommendations for cancer survivorship navigation from the American Society of Clinical Oncology (ASCO) and others. These resources include core navigation competencies for survivorship, patient assessment, scope of practice, etc. These trainings will be completed with additional focus areas/domains identified during the adaptation processes. Based on the structure of the existing PN program, we anticipate holding monthly review of navigation milestones and metrics (developed based on established recommendations and stakeholder input) with the study team.

Patient-level: For the pilot test in the UG3 phase, we will identify eligible patients from a single clinical site within KPSC. We anticipate enrolling 15-25 patients in the pilot. Patients will receive a letter and brochure describing the adapted AYA PN program with a bio of their assigned navigator and how the program will help integrate primary care and cancer survivorship needs. We strongly anticipate navigation 'touches' will include progressive steps via a combination of delivery modes as with the existing PN programs: 1) email: patients with KP.org patient portal accounts will receive email communication from navigators; 2) text: patients with registered mobile phone in KP membership files will receive text-based communications; 3) calls: patients will receive calls from their navigator to discuss scheduling, overdue recommended care, and motivational coaching; 4) letters: patients may receive letters if unable to be reached via email, text, and calls. Navigators will work with the electronic medical record (EMR) to identify need for recommended healthcare services and gaps in care, working with the care team to pend orders for physician review and work directly with the patient using motivational interviewing skills to encourage participation in care, address social needs, and identify care goals. PN program milestones, developed based on established recommendations for survivorship navigation metrics and the input from our adaptation processes, will likely include patients contacted, engagement activities, and pending orders for physician review for overdue services.

	System-level: As part of the UG3 phase, we will work closely with our partners to adapt the PN program to suit existing clinical needs and workflows. We will convene 2-3 focus groups with care teams (nurses/physicians/advanced practice providers) and department administrators (DAs) using a semi-structured focus group format. These groups will provide feedback on the team-based care focus for the PN program, how to integrate seamlessly into existing clinical workflows, suggestions for use and/or expansion of existing KPSC information technology (IT) tools (e.g., the Complete Care Model tools), and clinical needs of the patient population. Using adapted health IT tools, flags may be created for patients due for recommended services.
Study Duration*:	In the UG3 phase, the study will open enrollment for the prospective single-arm pilot study by month 18, after focus group data and program adaptation is complete. Completion of data collection for the pilot is estimated at month 24.
Participant Duration:	In the UG3 phase, the patients in the single site pilot will complete all study tasks by 6 months.

1.2 SCHEMA



1.3 SCHEDULE OF ACTIVITIES

Table 5. Milestones by Month, UG3 Phase							
	Months	1-4	5-8	9-12	13-16	17-20	21-24
Aim 1	Study approvals and start-up	X					
	IRB approval	X					
	Recruitment for focus groups		X				
	AYA Primary Care Council kick-off		X				
	Conduct focus groups, analyze data			X			
	Ongoing council meetings and PN program development			X	X	X	X
Aim 2	Navigation training				X		
	Pilot test				X	X	X
	Assessment of pilot (surveys, interviews)					X	X
	Finalize trial protocol						X

2 INTRODUCTION

2.1 STUDY RATIONALE

There is an urgent need to provide high-quality survivorship care to the rapidly growing population of adolescent and young adult (AYA) cancer survivors. Approximately 90,000 AYAs are diagnosed with cancer each year.[1,2] AYAs, defined as those diagnosed between 15-39 years of age, are at unique developmental life stages regarding their emotional, cognitive, and social development, and cancer diagnosis and treatment is highly disruptive to completing education, establishing families, and/or starting employment.[3,4] AYA cancer survivors have complex health care needs requiring coordinated care, including surveillance for cancer recurrence, management of long-term and late effects, and appropriate preventive care.[5-7] However, serious gaps in care have been identified for AYA survivors, including underuse of guideline-recommended cancer surveillance (e.g., mammography, colonoscopy) and specific screenings based on cancer treatment exposures,[8-14] as well as underuse of primary care services such as vaccinations and general disease screenings.[15,16] AYA cancer survivors bear a high burden of morbidity associated with chronic conditions and premature mortality, and there is an urgent need to provide ongoing, high-quality survivorship care to this population.[4] Our recent work found that one-quarter of AYA survivors had no oncology-related specialty visits within their first year after treatment despite guideline recommendations.[17] AYA survivors also experience significant disparities in care and outcomes associated with race, ethnicity, and socioeconomic status.[18,19]

High-quality, equitable, comprehensive AYA cancer survivorship care requires a team-based model of primary care with patient navigation. Cancer survivors actively managed in primary care that involved primary care received higher quality of care.[20-25] Team-based primary care with patient navigation has been shown to improve receipt of cancer screening, surveillance, and primary care services, particularly in underserved populations at higher risk for gaps in care.[26-32] Navigation programs address common barriers associated with health disparities (insurance and financial barriers, transportation, language, lack of social support),[33] and can also reduce unnecessary and unplanned care (e.g., emergency department visits, hospitalizations).[34] Unfortunately, primary care engagement can be low after AYA patients are

diagnosed with cancer[14] and there are few, if any, primary care-based patient navigation models of survivorship care focused on AYA cancer survivors.

Thus, despite the multitude of benefits shown by PN programs in the empirical literature, there are few, if any, primary care-based PN programs for AYA survivors, representing a critical gap. Our study will be one of the first to draw on implementation science methods to adapt and test a primary care-based PN program for AYA survivors. We will build on our expertise in cancer survivorship research, implementation and adaptation of evidence-based interventions, and pragmatic trial methods to apply a novel combination of frameworks, including RE-AIM,[35] the Framework for Reporting Adaptations and Modifications-Expanded (FRAME),[36] and Escoffery's 11 steps of adaptation[37] to adapt the existing navigation program in the UG3 phase of the study. In the UH3 phase, we will conduct a rigorous pragmatic stepped wedge hybrid type 2 trial of the program in 35 primary care clinics with a minimum of 850 AYA survivors, with pragmatic elements based on the PRECIS-2; the protocol will be updated appropriately upon award of the UH3 phase.[38]

2.2 BACKGROUND

We are nearing three-quarters of a million AYA cancer survivors in the U.S, and the population is growing rapidly.[39] Approximately 90,000 new cases of cancer in adolescents and young adults (AYAs) are diagnosed annually,[2] with AYA defined by the National Cancer Institute (NCI) and others as those diagnosed with cancer between 15-39 years of age. Increased incidence of colorectal, breast, endometrial, and other cancers among individuals under 40 is well documented.[1,2,40] Although causal mechanisms remain somewhat unclear, likely contributors to these increases include lifestyle factors, environmental factors, dietary and obesity trends, and changes in screening practices.[1,41,42] As AYAs diagnosed with cancer are living longer than ever, with 5- year relative survival of 86%,[43] the majority of these patients will enter into a prolonged post-treatment phase of care and are considered cancer survivors.[44] Cancer survivors require coordinated, comprehensive care addressing several domains of survivorship as described by National Academy of Medicine (NAM), ASCO and others, including surveillance for recurrence, screening for new cancers, screening for long-term and late effects of treatment, symptom management, and primary and preventive care.

AYA cancer survivors have multiple unmet healthcare needs and experience significant disparities in care. AYAs are at unique developmental and life stages regarding their emotional, cognitive, and social development, and cancer diagnosis and treatment is highly disruptive to establishing families, completing education, and/or starting employment.[3] AYAs face multiple unique challenges to accessing high-quality survivorship care, both at the system-level (e.g., transitioning from pediatric to adult-focused care, the need for care outside of typical clinic hours) and individual-level socioeconomic barriers (e.g., uninsured/underinsured, limited paid leave, caregiving for young children).[45-48] AYAs span diverse developmental life stages with varying needs; for example, younger AYAs report higher need for information and supportive care than older AYAs.[49,50] Other needs, such as fertility counseling and access to reproductive health services, are acknowledged as critically important across the AYA age span.[51] However, AYA survivors often have low uptake of guideline-recommended cancer surveillance services such as annual mammograms for breast cancer survivors and treatment exposure-based screenings.[14,52] Additionally, AYA survivors experience delayed or interrupted return to primary care and have low uptake of preventive care, including influenza vaccination, screening for non-primary cancers, and screening for hypertension and lipid abnormalities.[16,53] Health insurance and socioeconomic status have been shown to play a critical role in access to high-quality care and patient outcomes for AYA survivors.[18] In a large cohort of AYA patients diagnosed with cancer, there were significant disparities in relative survival by

race/ethnicity, poverty level, and insurance type.[19] Other studies have shown disparities in AYA survival by race/ethnicity;[54,55] for example, Black AYA patients diagnosed with colon cancer between 20-49 years had smaller increases in relative survival compared to White patients over time.[56] It is clear that improvements in access to and receipt of high-quality care are critically needed—and this is particularly acute for traditionally underserved populations.[3] Compounding these issues, our current oncology workforce is insufficient to care for the rapidly growing population of cancer survivors,[57-61] with a shortage of oncology physicians predicted by 2025[62] and concomitant oncology nursing shortage.[63] The current approach to delivering survivorship care, which is typically with oncology specialists with limited or no coordination with primary care providers or patient navigators, is inadequate and fails to meet the unique healthcare and psychosocial needs of AYA survivors.[64]

High-quality, equitable, and comprehensive AYA survivorship care requires patient navigation with team-based primary care. Primary care-based, coordinated survivorship care is critically important for provision of high-quality care to AYA cancer survivors.[65] Primary care-based teams are well-positioned to counsel survivors regarding lifestyle choices such as physical activity,[66] disease prevention,[67] screening for psychosocial health needs,[68] and tobacco cessation.[69] Recent studies have found that the majority of healthcare received by cancer survivors comes from primary care,[70] and that primary care teams feel they have a significant role to play in cancer survivorship.[71-73] However, there are considerable barriers to time-pressed primary care physicians involvement in survivorship, including resources, knowledge, and systems- level support, and it is not sustainable to continually ask our primary care physicians to simply "do more."[74-78] A team-based approach with comprehensive patient navigation offers demonstrated potential for optimizing AYA survivor outcomes. Patient navigation (PN) is defined as individualized assistance offered to patients and families to help overcome barriers to care and optimize health outcomes, and navigators have been described as "catalysts to mitigate cancer disparities."[79] A rich PN literature has been developed over the past two decades including multiple systematic reviews and meta-analyses,[26-30] demonstrating PN can improve a variety of clinical outcomes, particularly in underserved populations at higher risk for gaps in care.[31] Primary care-based PN programs have been shown to improve patient access and connection to appropriate clinicians, improve patient-provider communication, increase interaction and links with the health system, increase patient employment, reduce financial stresses, and improve insurance coverage.[80,81] PN also improves cancer-related care, including symptom management,[28,82,83] increases timely cancer diagnostic resolution and follow-up, and leads to higher completion rates for cancer screenings and treatment as well as higher rates of attending medical appointments.[34,84] PN addresses common barriers to access associated with health disparities, coordination, transportation, language, and lack of social support.[33] A recent review concluded that PN also reduces unnecessary or unplanned care (e.g., emergency department utilization, hospitalization), can reduce burden for physicians, and are cost-effective.[34] Although limited in number, PN survivorship programs have shown improvements in guideline-recommended cancer surveillance services and health-reported quality of life.[85-87] Navigators use elements of care coordination and can be considered a type of coordinator, based on the definition from the Alliance to Advance Patient-Centered Cancer Care ("Patient navigation represents an evidence-based health care intervention designed to enhance patient-centered care and care coordination")[88] as well as recent meta-analyses and reviews of the navigation and coordination literature.[27,89] Given this large body of research, PN is clearly an evidence-based intervention suitable for widespread implementation. Recent in-depth qualitative work from our research group focused on developing a comprehensive model of AYA survivorship found that AYA survivors strongly encourage use of PN programs tailored to their needs.[90] However, only a small number of PN studies have focused on the AYA survivor population, mainly centered around preferences for PN programs rather than adaptation, implementation, or sustainment.[51,91,92]

Results from this study will yield valuable evidence on the effectiveness and mechanisms of effect of a scalable, adaptable primary care-based patient navigation program targeting AYA cancer survivors, addressing the critical need to improve the quality of care for this unique patient population.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

For this study, a waiver of informed consent and HIPAA authorization waiver will be required to identify KPSC AYA cancer survivors by condition who are eligible for enrollment into the adapted PN program pilot and focus group recruitment sample (UG3 phase). We do not foresee any risks to potential participants by not directly consenting them to participate for identification by condition. It will be prohibitive to contact patients directly for identification by condition and this study poses no more than minimal risk to privacy and confidentiality of study participants. Survivorship cancer care will be performed as part of routine medical care that is consistent with guidelines from professional societies and organizations. The pilot adapted PN program will focus on directing enrolled AYA patients to guideline-recommended services that already exist, essentially bridging service gaps for this population. In addition, participation in the adapted PN program (UG3 phase) will be voluntary. We also believe that such a waiver of consent is not only widely recognized as necessary and appropriate, but also scientifically necessary and ethically justifiable under the "Common Rule" for protection of research participants (45 CFR 46.116d) – (e.g., 1) the research involves no more than minimal risk to the subjects; 2) the waiver of alteration will not adversely affect the rights or welfare of the subjects; 3) the research could not practicably be carried out without the waiver of alteration; and 4) whenever appropriate, the subjects will be provided with additional pertinent information after participation in the form of a summary sheet of survey findings after completion of the study). Throughout the study phases, we will work closely with our Institutional Review Board (IRB), clinical chiefs, and operational leaders to ensure patient safety, with regular review and reporting of adverse events and protocol deviations.

Patients, clinicians and administrators will be individually recruited for focus groups and surveys and we will obtain written or oral consent from all participants, unless we obtain approval from the KPSC IRB for a waiver of written informed consent for these specific study-related activities.

A rare but serious harm that could occur is loss of confidentiality of personal health information (PHI), but every effort will be made to protect PHI. Specifically, each focus group and survey participant will be given a unique alpha-numeric identification number. No data collection form will be linked to an actual participant name. Any document linking the participant's name to an identification number will be kept in a locked file separate from data collection files. All records from the study will be kept in locked files. Identifying information will be removed from the final data sets and stored in a linked file to which only the Principal Investigator (PI) or designee has access. Individual participants will not be identified in any reports. Additionally, study reports will be aggregated so that individual participants are not identified. All investigators and research staff at participating sites will be required to maintain up-to-date training in human subject protection and good clinical practice through Collaborative Institutional Training Initiative (CITI; https://about.citiprogram.org/) and HIPAA training. Additional security precautions include encryption, digital certification, audit logs, and firewall protection.

2.3.2 KNOWN POTENTIAL BENEFITS

There are no direct benefits to the participants in this proposed study. There are potential societal benefits from our findings. Our study is innovative, among the first to draw on implementation science methods to adapt and test a primary care-based PN program for AYA survivors. Despite recognition of the unique needs of AYA survivors and critical gaps in primary, preventive, and surveillance care, there has been little rigorous investigation of barriers and methods for adaptation and implementation of primary care-based PN programs for AYA survivors. Several initiatives are underway to improve awareness of AYA survivor needs and provide education to clinicians and survivors about recommended care, many of which rely of mHealth solutions; however, recent reviews have highlighted that these studies have been small, single-arm studies mainly focusing on feasibility.[93-96] Our proposed study will add to the evidence base for primary care-based navigation services tailored for AYA cancer survivors, potentially leading to policy decisions regarding coverage and reimbursement from private insurers and Medicaid as well as care delivery decisions by capitated healthcare delivery systems.

Ultimately, results from this study will yield valuable evidence on the effectiveness and mechanisms of effect of a scalable, adaptable primary care-based patient navigation program targeting AYA cancer survivors, addressing the critical need to improve the quality of care for this unique patient population.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

There are minimal physical, psychological, social, legal, privacy or other risks from participating in this study. Individual patients and clinicians will not be recruited for enrollment into the adaptive PN pilot (UG3 phase) or the stepped-wedge trial (UH3), thus there is minimal risk to loss of privacy or confidentiality; any demographic, clinical and utilization data will be collected from the EMR and/or claims data with no participant interaction. A rare but serious harm that could occur is loss of confidentiality of PHI. However, participant confidentiality will be maintained at all times using the specific steps and procedures for enrollment, focus groups and surveys, as outlined in **Section 2.31** above.

3 OBJECTIVES AND ENDPOINTS

We have defined measurable, feasible milestones for both the UG3 and UH3 phases of the study. **The UG3 phase has been awarded for two years; upon successful completion of this phase, the NCI will provide funding for the second phase of the study, which will allow our team to conduct the pragmatic stepped wedge hybrid 2 effectiveness-implementation trial outlined in this protocol (UH3 phase). Herein we are focusing on the UG3 phase, with reference for future protocol versions that incorporate the UH3 phase once awarded.**

We will engage in a three-step process to achieve our goals for the UG3 phase:

1. Intervention refinement via context assessment including multilevel barriers and facilitators to guide adaptation; adaptation and tailoring to local contexts.
2. Demonstrate feasibility of program implementation with pilot testing of recruitment, data collection, evaluation plans and methods, and data sources.

3. Develop and demonstrate the feasibility of logistical and administrative arrangements for conducting the pragmatic trial in the UH3 phase including finalizing agreements with sites, IRB approvals, and development of a manual of operations for the trial.

In **step 1**, we plan for rigorous exploration and documentation of adaptation processes via a combined use of implementation and adaptation frameworks, representing a significant contribution to the field. Intentional adaptation provides an opportunity for implementation flexibility, potentially improving the overall fit of an evidence-based intervention to a new population and/or context,[97] such as AYA survivors care in the primary care setting. Several adaptation frameworks have been proposed over the past decade, with a collective recognition of the importance of rigorous research on adaptation processes and the distinction between the function (e.g., core elements) and form (e.g., delivery type) of evidence-based interventions.[98] We will follow the overarching steps of adaptation processes as described by Escoffery et al.,[37] consisting of eleven discrete steps, with extensive stakeholder engagement throughout. We will supplement this with a novel application of the RE-AIM framework for guidance on the 'who, why, how' of adaptation a nascent and exciting application of RE-AIM to adaptation processes. We will use the FRAME to guide thorough documentation of adaptation activities throughout the eleven steps. This blend of Escoffery's eleven steps, RE-AIM, and FRAME provides a stepwise, thoughtful approach for capturing the rationale for adaptation, the internal and external context of adaptation, and for cataloguing adaptation elements (see Section C.5.3 for adaptation process details). Recent work from leaders in the field have combined RE-AIM with adaptation frameworks,[99,100] although not in this specific combination which is more appropriate to address our research questions. We propose a multilevel adaptation process, tailoring PN program components to meet the needs of AYA cancer survivors, primary care teams, and the organizational setting (and leveraging available supportive resources). We will be adapting KPSC's existing PN program for patients newly diagnosed with cancer, which includes KPSC's robust 'Complete Care' model and health IT tools shown to be effective at managing cancer (diagnosis and initial treatment) and other chronic conditions.[101,102] In **step 2**, we will conduct a pilot study of the adapted PN program with a single clinic, collecting patient, clinician, and clinic-level data and iteratively refining the PN program as appropriate. Following Escoffery's Eleven Steps of Adaptation, we will: 1) assess community, 2) understand the intervention (patient navigation program), 3) select the appropriate program structure, 4) consult with experts, 5) consult with stakeholders, 6) decide on needed adaptations, 7) adapt, 8) train staff, and 9) pilot test the adapted materials. Lastly, in **step 3** we will develop our trial manual of operations and obtain administrative and other approvals so that the trial is set to launch at start of Year 3.

In the UH3 phase, we will conduct a pragmatic stepped wedge hybrid type 2 effectiveness-implementation trial with extensive quantitative and qualitative process evaluation activities to examine mechanisms of effect, moderators and other contextual factors.[103] This protocol will be updated once the UH3 phase is awarded.

Primary Outcomes: UG3

We will conduct a prospective, single-arm pilot study of the adapted AYA PN program at a participating clinic site in Southern California, focusing on the *perceptual implementation outcomes* of acceptability, appropriateness, and feasibility (the *behavioral implementation outcomes* including adoption, penetration, fidelity and sustainment will be measured in the UH3 pragmatic trial) and the hypothesized PN program outcomes of increased motivation, capability, and opportunity for care. The pilot will also include testing of patient enrollment/engagement methods, clinical workflow, survey recruitment methods, and health IT elements (e.g., access, ease of use). We anticipate enrolling 15-25 AYA survivors.

Survey Measures. While there is no single measure of PN programs, there are several measures that address the theorized PN mechanisms of motivation, capability, and opportunity for care; these domains are commonly conceptualized as patient satisfaction with care, receipt of care, barriers and facilitators to care, and self- efficacy or 'health competence.' As described over a decade ago by Fiscella et al there are several patient- reported outcomes appropriate for measuring the impact of PN programs. Based on those specific recommendations for measuring cancer survivorship PN programs, **patient surveys** will include a validated measure of self-efficacy (the Perceived Health Competence Scale), measures of care coordination and communication from the Care Coordination Quality Measures developed by the Agency for Healthcare Research and Quality (AHRQ), and measures of barriers to care (e.g., non-adherence due to cost, access issues) and provider communication from the Medical Expenditure Panel Survey (MEPS). The MEPS patient-provider communication scale evaluates discussions about: 1) cancer follow-up care; 2) late or long- term treatment effects; 3) lifestyle recommendations; and 4) emotional or social needs. While other measures may offer more comprehensive scales of these domains, we wish to be mindful of participant time and likelihood of participation based on survey length and will therefore limit to these most highly relevant measures. Patient surveys will also include questions on ways to improve or change the PN program elements as well as contact and engagement methods for patients.

Clinician and administrator surveys will include questions on ease of clinical workflow integration, familiarity with the PN program, and open-ended questions on ways to improve the PN program from a clinical or administrative perspective. **Both patient and clinician/administrative surveys** will include validated measures of acceptability, appropriateness, and feasibility of the PN program, developed by Weiner et al, as well as questions about survey contact methods and reasons for participation and hypothesized reasons for non-participation (e.g., "*Why do you think someone would decide not to participate in this survey?").* This will help refine the survey outreach for the UH3 pragmatic trial.

Survey Recruitment Methods. We will invite all AYA survivors contacted as part of the pilot as well as clinical team members and the clinic's administrative team to participate in survey after their introduction to the PN program. We will use Dillman's Tailored Design Method[104] to guide all survey activities with goals to: 1) Minimize all possible sources of survey error; 2) Tailor to the survey population; and 3) Use procedures that create positive social exchange and encourage response. We designed our REDCap-based recruitment procedures to encourage response and minimize nonresponse by using multiple modes of contact, multiple modes of response (e.g., direct link to web survey, paper survey), and incentives. Patient participants will receive a $20 gift card for completing the survey, as evidence suggests this is one of the best ways to improve response rates and increase representativeness.[104,105] Mixed-mode strategies such as the one we propose have been shown to be effective and help minimize total survey error. We will engage our Advisory Board to refine recruitment materials.

Data Collection and Analysis. We will invite AYA patients contacted by the program and clinical staff and administrators to complete brief electronic surveys. We will collect demographic information (e.g., age, race, ethnicity, census-level education and income) and clinical information (e.g., date of cancer diagnosis, age at diagnosis, disease stage, cancer treatment type, tumor genomics) from the EMR and tumor registry for all participants. We will collect for clinician variables such as gender, race, and years in practice from the EMR. Sex as a potentially important biologic factor will be included in all analyses. Use of existing data in the EMR can other databases is in alignment with the highly pragmatic nature of the trial.

We will create descriptive summary tables of results. We did not do a formal power analysis for the pilot data, as this will be only one clinic site and the purpose is to identify areas needing additional refinement prior to the launch of the pragmatic trial.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS	PUTATIVE MECHANISMS OF ACTION
Primary			
UG3 Phase. Adapt a navigation program to suit the needs of the AYA cancer survivor population. Conduct a prospective single arm pilot study of the adapted AYA PN program.	Patient outcome measures taken pre/post entry into the navigation program include self-efficacy, care coordination and communication from the Care Coordination Quality Measures developed by the Agency for Healthcare Research and Quality, and measures of barriers to care (e.g., non-adherence due to cost, access issues) and provider communication from the Medical Expenditure Panel Survey. **Clinician and administrator surveys** will include questions on ease of clinical workflow integration, familiarity with the PN program, and open-ended questions on ways to improve the PN program from a clinical or administrative perspective. **Both patient and clinician/administrative surveys** will include validated measures of acceptability, appropriateness, and feasibility of the PN program (perceptual implementation outcomes).	We hypothesize that the patient navigation program will increase patient capability, motivation and opportunity to connect to the healthcare system. Thus, we include measures of self-efficacy, perceived care coordination, and communication. Other survey measures will help guide the refinement of the program for the UH phase.	
Secondary			

4 STUDY DESIGN

4.1 OVERALL DESIGN

The purpose of the study is to: 1) Adapt an evidence-based cancer-focused patient navigation program to the AYA survivor population; and 2) Plan and conduct a pragmatic stepped wedge hybrid type 2 effectiveness-implementation trial of this program within KPSC. We will apply a novel combination of frameworks, including RE-AIM, the Framework for Reporting Adaptations and Modifications-Expanded (FRAME), and Escoffery's steps of adaptation to adapt the existing navigation program and conduct a rigorous pragmatic stepped wedge hybrid type 2 trial of the program with pragmatic elements based on

the PRECIS-2. Here we describe the initial funded phase of the study (the UG3 phase) which is a 2-year adaptation process and single-arm prospective pilot study of the adapted patient navigation program.

UG3 Aim 1. Adapt and tailor an existing patient navigation program to meet the needs of AYA cancer survivors and the local clinical context via (a) qualitative research involving key stakeholders (patients, clinicians, administrators) and (b) guidance from our AYA Primary Care Survivorship Council.

UG3 Aim 2. Pilot and refine the program to enhance acceptability to patients and clinicians, enhance feasibility and effectiveness, and develop and pilot pragmatic trial evaluation tools and methods.

The pilot study will focus on AYA patients 3-36 months post-diagnosis, allowing for the PN program to reach patients coming into early post-treatment survivorship as well as those who have completed treatment within the past 12-24 months (assuming an average treatment time of 6-18 months for these tumor types). Thus, we will prospectively identify AYA cancer patients with 10 disease types and diagnosed with local/regional disease undergoing treatment or in survivorship at study start. The top 10 most diagnosed local and regional solid tumors in the AYA age range, based on data from the KPSC SEER-affiliated cancer registry: breast, ovarian, cervical, testicular, colon/rectal, melanoma, endometrial, sarcoma, and thyroid cancers. In line with the pragmatic design, we have kept a very broad eligibility criteria and minimized exclusions to enhance the generalizability of results. There are no exclusions based on sex, race/ethnicity, comorbidity status, lifestyle factors (e.g., tobacco and alcohol use), or other patient demographics. We will not include leukemia and lymphoma patients as these patients are often cared for in the inpatient setting and/or transferred to tertiary cancer centers for transplant. We also exclude patients with metastatic disease at diagnosis, as these patients are cared for within an integrated palliative care/oncology/social work team structure starting at diagnosis, and the addition of the PN program would be providing duplicative services. Lastly, we will exclude patients with less than 120 days of Kaiser Permanente insurance membership after diagnosis of primary cancer, as we would not be able to follow the patient into their cancer survivorship phase.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Following the structure of the NCI two-phase cooperative agreement, we propose to: 1) Adapt an existing evidence-based, cancer-focused PN program to the AYA survivor population and to the clinical setting; and 2) Conduct a pragmatic stepped wedge hybrid type 2 effectiveness-implementation trial within a large integrated healthcare system, KPSC. As described in established program theory for patient navigation, we hypothesize that the adapted PN program will lead to increased uptake of high-quality, guideline-recommended primary care and cancer surveillance services for AYA survivors (clinical outcomes), and high levels of acceptability, appropriateness, feasibility, adoption, penetration, fidelity, and sustainment (Proctor's implementation outcomes). In the UG3 phase, we will focus on three areas derived from the scientific literature on navigation and adaptation of evidence-based interventions:

1. Intervention refinement via context assessment including multilevel barriers and facilitators to guide adaptation; adaptation and tailoring to local contexts.
2. Demonstrate feasibility of program implementation with a prospective single-arm pilot study.
3. Develop and demonstrate the feasibility of logistical and administrative arrangements for conducting the pragmatic trial in the UH3 phase including finalizing agreements with sites, IRB approvals, and development of a manual of operations for the trial.

4.3 JUSTIFICATION FOR INTERVENTION

There is a rich body of evidence from over 2 decades of scientific inquiry demonstrating the effectiveness of patient navigation (PN) on improving patient outcomes, increasing access to and receipt of care (particularly in underserved populations), and lowering costs,[26-30] experts have called for greater focus on PN programs specifically for cancer survivors. A recent systematic review of cancer PN programs notes that 50% of programs focused on cancer screening only and an additional 27% on cancer diagnosis only.[84] As noted in a recent editorial on community navigation programs for cancer patients, despite the evidence of success of PN programs, deploying these complex multilevel interventions is challenging and a successful program requires adaptation and tailoring to meet cultural, economic, patient, and health-system needs.[106]

High-quality, equitable, comprehensive AYA cancer survivorship care requires a team-based model of primary care with patient navigation. Cancer survivors actively managed in primary care that involved primary care received higher quality of care.[20-25] Team-based primary care with patient navigation has been shown to improve receipt of cancer screening, surveillance, and primary care services, particularly in underserved populations at higher risk for gaps in care.[26-32] Navigation programs address common barriers associated with health disparities (insurance and financial barriers, transportation, language, lack of social support),[33] and can also reduce unnecessary and unplanned care (e.g., emergency department visits, hospitalizations).[34]

Thus, despite the multitude of benefits shown by PN programs in the empirical literature, there are few, if any, primary care-based PN programs for AYA survivors, representing a critical gap. This paucity of high-quality implementation research, particularly in community-based settings, seriously limits our ability to implement policy or practice decisions regarding optimal survivorship care delivery for the growing AYA survivor population. Our study will be one of the first to draw on implementation science methods to adapt and test a primary care-based PN program for AYA survivors. Medicare recently announced payment changes including offering reimbursement for navigation services given the strong evidence of benefit from PN programs.[107] Although limited to older adults, this demonstrates the power of high-quality research to affect policy decisions. Thus, our program of research to adapt and test an evidence-based PN program for AYA cancer survivors is highly justified and has a high likelihood of success.

4.4 END-OF-STUDY DEFINITION

In the UG3 phase, a participant is considered to have completed the study if he or she has:

- Participated in a one-time focus group; or
- Participated as a patient in the prospective, single-arm pilot study for 6 months and completed the associated survey; or
- Participated as a clinician and/or administrator in the one-time survey about the navigation program.
- For patient data, truncated person-time will be accounted for in case of membership end or death during the pilot study.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

Patient Population Selection for UG3:
Patient Identification for Focus Group Recruitment. KPSC AYA cancer survivors who fit study eligibility will be identified from our KPSC cancer registry.

Clinician and Administrator Focus Groups. Nurses, physicians, advanced practice providers and administrators will be identified from the primary care teams at our participating five sites.

Inclusion Criteria:

Patient Focus Groups. Inclusion criteria: (1) Aged 15-39** years old at time of cancer diagnosis; (2) a diagnosis of breast, ovarian, cervical, testicular, colon/rectal, melanoma, endometrial, sarcoma, or thyroid cancers; and (3) up to 6 years post-treatment.

Clinician and Administrator Focus Groups. Physicians selected to participate must be Board Certified in Internal or Family Medicine, hold a valid and current MD and be employed by the Southern California Permanente Medical Group. Nurses or Advanced Care Practitioners must hold a valid license and be employed by Kaiser Permanente Southern California. Department Administrators must be employed by Kaiser Permanente Southern California.

Single-arm prospective pilot study:
Inclusion criteria: (1) Aged 15-39** years old at time of cancer diagnosis; (2) a diagnosis of breast, ovarian, cervical, testicular, colon/rectal, melanoma, endometrial, sarcoma, or thyroid cancers; and (3) up to 36 months post-diagnosis.

***While we will be identifying patients from our cancer registry that were diagnosed with cancer between 15-39 years of age, for the pilot (Phase 1) and potential future trial (Phase 2) we will be focusing only on those patients who are now over the age of 21; therefore we will not be enrolling patients under the age of 18 years nor including them in focus groups or surveys. The rationale is that younger patients tend to stay within pediatric oncology for extended periods and would not likely benefit from our intervention.*

5.2 EXCLUSION CRITERIA

Exclusion criteria for UG3:

- Patients with a history of leukemia or lymphoma.
- Patients with metastatic disease at diagnosis
- Patients with less than 120 days of Kaiser Permanente insurance membership after diagnosis of primary cancer

5.3 LIFESTYLE CONSIDERATIONS

N/A

5.4 SCREEN FAILURES

The study focuses on patients diagnosed with local and regional solid tumors in the AYA age range, based on data from the KPSC SEER-affiliated cancer registry: breast, ovarian, cervical, testicular, colon/rectal, melanoma, endometrial, sarcoma, and thyroid cancers. In line with the pragmatic design, we have kept a very broad eligibility criteria and minimized exclusions to enhance the generalizability of results. There are no exclusions based on sex, race/ethnicity, comorbidity status, lifestyle factors (e.g., tobacco and alcohol use), or other patient demographics.

We will prospectively identify AYA cancer patients with the 10 disease types described above and diagnosed with local/regional disease undergoing treatment or in survivorship at study start. We will use our comprehensive pathology database, Co-Path, combined with an EMR text-information extraction system and cancer registry data to identify eligible patients. Breast cancer patients may be receiving ongoing HER-2 directed therapy or endocrine therapy and be considered eligible for the PN program.

Screen failures are defined as participants misidentified either by age at diagnosis (i.e., not diagnosed within the AYA age range) or by disease stage—those who did not have local or regional disease at time of diagnosis (i.e., metastatic disease at diagnosis). Misidentified patients will be considered screen failures, will be excluded from the study, and will receive their survivorship care under usual care conditions.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Recruitment UG3 phase

A waiver of the requirement for informed consent will be requested for enrollment into the PN program for the pilot study. We believe that such a waiver of consent is not only necessary and appropriate, given the proven track record and evidence base of PN programs, but is also scientifically necessary and ethically justified given the minimal risk of the proposed research based on the Common Rule, 45 CFR 46.116d (e.g., use of routine care practices, no investigational drugs or devices, little risk of physical or psychological harm).This also allows for the AYA PN program to be integrated into usual care processes for the clinic, simplifying the research participation processes and maximizing our patient contact, engagement, and generalizability of results.

Patient Focus Groups. Using a REDcap recruitment and tracking database, we will send an initial recruitment email to a batch of the potential participants (approximately 25-30) describing the study and invite the recipients to participate in the focus group. Follow-up contacts will be made using multi modal outreach (e.g., emails, texts, letters). We will randomly select the initial batch of patients using a SAS-generated algorithm. Once we have exhausted the initial batch without reaching our recruitment goal, we will identify a second batch of potential participants (approximately 25-30) and continue with batches until our recruitment goals are reached. Focus groups will be conducted either online or in person at the Kaiser Permanente clinical research center (Pasadena, CA) equipped with a focus group facility or at a professional focus group room rented in the community.

Provider and Administrator Focus Groups. For clinicians and administrators, we will follow a similar recruitment protocol although we will restrict recruitment outreach to email contact. Our studies that have involved clinicians and administrators in qualitative research have found that this group responds to

email contact attempts but are much less likely to respond to letter or phone recruitment contacts. Focus groups will be conducted either online (e.g., Microsoft TEAMS) or in-person.

Estimated participant time commitment:

We estimate a total time commitment for both AYA patients and providers participating in focus groups to be approximately 4 hours.

Compensation amount and type:

Patient Focus Groups. Patients will receive a $150 gift card upon completion of the focus group. If focus groups are conducted in person, food and beverages will also be provided.

Clinician and Administrator Focus Groups. Clinicians and administrators will not receive renumeration for their participation in the focus group. However, if focus groups are conducted in person, food and beverages will be provided.

6 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S)

6.1 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION OR EXPERIMENTAL MANIPULATION DESCRIPTION

Intervention for UG3 pilot study. The intervention for this phase of the study will be based on the adapted AYA PN program developed under the UG3 initial phase activities. The proposed multilevel adaptations will be based on the existing KPSC PN program for patients newly diagnosed with cancer, which was developed using PN program theory and incorporates the core functions of **enhancing patient capability, motivation, and opportunity for care**. However, the current KPSC PN cancer program does not extend into cancer survivorship; rather, it focuses on guiding newly diagnosed patients through the initial steps of diagnostic procedures (e.g., imaging, labs), scheduling and referral for cancer treatment (surgery, medical oncology), and provision of education and support through the initial stages of cancer treatment. Therefore, the adapted AYA PN cancer survivorship program will adhere to these core functions, but we anticipate that the adapted PN program will have refinements to the forms of these core functions, including mode of delivery, outreach timing and tone, clinical workflow, and survivorship domains of care (e.g., cancer surveillance, screening for late effects). For the AYA PN program, we will adapt the current health IT tools highlight or flag the relevant National Comprehensive Cancer Network (NCCN) and USPSTF guideline recommendations. The navigation intervention may also use existing IT tools such as the Proactive Office Encounter (POE) which is the EMR alert system for overdue recommended care, and the KPSC 'cancer tracker' system for newly diagnosed patients. These tools will allow for close collaboration between navigators and oncology and primary care teams, addressing gaps in care without duplication of effort. We will establish a shared-care protocol to ensure that services are not duplicated.

6.1.2 ADMINISTRATION AND/OR DOSING

Intervention: Navigators

Navigators will undergo a comprehensive training curriculum that draws on existing KPSC trainings and includes primary care and cancer survivorship/surveillance components and established recommendations for cancer survivorship navigation from ASCO and others. These resources include core navigation competencies for survivorship, patient assessment, scope of practice, etc. These trainings will be completed with additional focus areas/domains identified during the adaptation processes. Based on the structure of the existing PN program, we anticipate holding monthly review of navigation milestones and metrics (developed based on established recommendations and stakeholder input) with the study team, and at least quarterly with the primary care team within the clinic.

Intervention: Patients
All eligible patients at a single clinical site will be passively enrolled in the PN pilot study. Patients will receive a letter and brochure describing the adapted AYA PN program at the start of the assigned stepped wedge phase, with a bio of their assigned navigator and how the program will help integrate primary care and cancer survivorship needs. We strongly anticipate navigation 'touches' will include progressive steps via a combination of delivery modes as with the existing PN programs: 1) email: patients with KP.org patient portal accounts will receive email communication from navigators; 2) text: patients with registered mobile phone in KP membership files will receive text-based communications; 3) calls: patients will receive calls from their navigator to discuss scheduling, overdue recommended care, and motivational coaching; 4) letters: patients may receive letters if unable to be reached via email, text, and calls. Navigators will work with the EMR to identify need for recommended healthcare services and gaps in care, working with the care team to pend orders for physician review and work directly with the patient using motivational interviewing skills to encourage participation in care, address social needs, and identify care goals.

Intervention: System-level
We will work closely with care teams in our participating service areas and clinics to adapt the PN program to suit clinical needs and workflows. We will include department administrators (DAs), who oversee staffing, IT needs, clinic management, and organizational goals. To deepen these insights, we will convene 2-3 focus groups with primary care teams (nurses/physicians/advanced practice providers) and DAs using a semi-structured focus group format. These groups will provide feedback on the team-based care focus for the PN program, how to integrate seamlessly into existing clinical workflows, suggestions for use and/or expansion of existing KPSC IT tools (e.g., the Complete Care Model tools), and clinical needs of the patient population.

Using adapted health IT tools, flags will be created for patients due for recommended services. Flags will also be created for unplanned hospitalizations and emergency department utilization to allow the navigators to connect with patients to offer support and assistance with care coordination during unplanned care episodes. These tools will allow for close collaboration between PCPs, navigators, and oncology teams.

6.2 FIDELITY

6.2.1 INTERVENTIONIST TRAINING AND TRACKING

For the UG3 pilot study, navigator training will be overseen by the study team. Subsequent navigation activities will include the development of relevant PN program milestones, developed based on established recommendations for survivorship navigation metrics and the input from our adaptation processes. These will likely include patients contacted, timing of contacts, engagement activities (e.g., use of motivational interviewing, PMT documentation in the EMR), pending orders for physician review for overdue services (e.g., labs, imaging related to cancer surveillance or primary care needs). Monthly review of navigation milestones and metrics will be discussed in study team meetings, and navigators will meet at least quarterly with the care team in the clinic to review patient metrics.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

N/A

6.4 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION ADHERENCE

For the UG3 pilot study, we will track patient participant contacts with the navigator (e.g., emails, phone calls). While there is no set number of 'correct' patient contacts, we anticipate all patients to have at least one contact to be considered adherent. Patient participation in the survey will be tracked and response rates calculated, although survey participation will not be required to participate in the navigation program..

6.5 CONCOMITANT THERAPY

N/A

6.5.1 RESCUE THERAPY

N/A

7 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

When a subject discontinues from the AYA PN cancer survivorship program but not from the study, remaining study procedures will be completed as indicated by the study protocol. If a clinically significant finding is identified after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

The data to be collected at the time of study intervention discontinuation will include the following:

- The reason(s) for discontinuing the participant from the intervention, and methods for determining the need to discontinue
- Where the participant will be receiving survivorship care.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the pilot study at any time. An investigator may discontinue a participant from the study for the following reasons:

- Significant study intervention non-compliance, unless varying compliance is an aspect of the study objectives;
- Lost-to-follow up; unable to contact subject (**see Section 7.3, Lost to Follow-Up**)
- Any event or medical condition or situation occurs such that continued collection of follow-up study data would not be in the best interest of the participant or might require an additional treatment that would confound the interpretation of the study;
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF). Subjects who receive the study intervention, and subsequently withdraw, or are discontinued from the study, will not be replaced.

7.3 LOST TO FOLLOW-UP

We will track all utilization within KPSC until disenrollment from KP health insurance or death.

For focus groups and surveys, a participant will be considered lost to follow-up if he or she does not respond to multiple contacts to complete the survey and/or focus group after agreeing to do so.

The following actions must be taken if a participant fails to complete the focus group interview or return the survey:

- The site will attempt to contact the participant or resend the survey, and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant. These contact attempts will be documented in the participant's study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study aim with a primary reason of lost to follow-up.

For the pilot study, a patient will be considered lost to follow-up if the following:

- We attempt to contact the participant, reschedule the missed contacts, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts will be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 ENDPOINT AND OTHER NON-SAFETY ASSESSMENTS

UG3 pilot study

Patients will complete brief surveys of key domains relating to patient navigation services: self-efficacy (the Perceived Health Competence Scale), measures of care coordination and communication from the Care Coordination Quality Measures developed by AHRQ, and measures of barriers to care (e.g., non-adherence due to cost, access issues) and provider communication from the MEPS. The MEPS patient-provider communication scale evaluates discussions about: 1) cancer follow-up care; 2) late or long-term treatment effects; 3) lifestyle recommendations; and 4) emotional or social needs. While other measures may offer more comprehensive scales of these domains, we wish to be mindful of participant time and likelihood of participation based on survey length and will therefore limit to these most highly relevant measures. Patient surveys will also include questions on ways to improve or change the PN program elements as well as contact and engagement methods for patients.

Clinician and administrator surveys will include questions on ease of clinical workflow integration, familiarity with the PN program, and open-ended questions on ways to improve the PN program from a clinical or administrative perspective.

Both patient and clinician/administrative surveys will include validated measures of acceptability, appropriateness, and feasibility of the PN program, developed by Weiner et al, as well as questions about survey contact methods and reasons for participation and hypothesized reasons for non-participation (e.g., "*Why do you think someone would decide not to participate in this survey?").* This will help refine the survey outreach for the UH3 pragmatic trial.

Navigation activities will be tracked with number of contacts, mode of contact, timing of contact, number of pended orders, and other metrics reviewed monthly and consolidated.

8.2 SAFETY ASSESSMENTS

Collection of observational data from administrative and clinical databases, self-reported demographics from the PRO surveys, and intervention activities at the KPSC medical centers will be collected and discussed at weekly project meetings. During monthly investigator meetings, data and recruitment summary reports of demographic and clinical information will be presented. Recruitment strategies will be brainstormed for optimization as needed. Recruitment success by racial/ethnic categories will be monitored closely and reported in National Institutes of Health (NIH) progress reports and to the Project Officer (PO) and/or Safety Monitoring Board (DSMB) no less than annually.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS

We believe this study poses no more than minimal risk to subjects and the protocol uses the definition of adverse event (AE) from the KPSC IRB: (a) any unfavorable medical or psychological events experienced by a study participant during clinical research, including: a) a new symptom; b) worsening of an existing condition; or a clinically significant abnormal lab finding. AEs are considered a reportable unanticipated problem (UP) -- e.g., reportable to the KPSC IRB -- if they meet all three criteria for an unanticipated problem:

- Unexpected in nature, severity, or frequency
- Related or possibly related to participation in the research
- Suggests greater risk to participants or others than previously known

Patients with local and regional cancer who survived their cancer therapy and are at least 1 year out from diagnosis will be enrolled in the pilot study. The pilot study time interval is quite short (estimated 6 months) and the intervention is unrelated to a drug or device; thus, it is unlikely that many patient participants will have a significant adverse event related to the pilot study.

In the event that an AE is determined, it must be reported to the IRB within 10 business days and at the continuing review period.

AE/SAE Attribution Scale. We will calculate overall rates of occurrence of SAEs (number of SAEs per person-month) by extracting EMR/administrative data monthly to identify signals that might indicate potential harm.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS

As defined by the KPSC IRB, a serious adverse event (SAE) includes:

- Death
- Life threatening condition/situation
- An enduring or significant incapacity or substantial disruption of the ability to conduct normal life functions
- The delivery of a child with congenital anomaly or birth defect
- Other medical events that the PI determines require intervention to prevent the above outcomes

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

The PI must take action to protect the study participant(s) or others from the unexpected risk of harm. For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity:

- **Mild** - Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the intervention measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

All AEs will have their relationship to study procedures, including the intervention, assessed by an appropriately trained clinician based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Related** – The AE is known to occur with the study procedures, there is a reasonable possibility that the study procedures caused the AE, or there is a temporal relationship between the study procedures and the event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study procedures and the AE.
- **Not Related** – There is not a reasonable possibility that the study procedures caused the event, there is no temporal relationship between the study procedures and event onset, or an alternate etiology has been established.

8.3.3.3 EXPECTEDNESS

The PI will determine if the event or incident is unexpected in nature, severity, or frequency, taking into consideration:

- The protocol-related documents, including: 1) IRB-approved research protocol or research application; or 2) other sources of information
- The PI's knowledge of the characteristics of the study population
- The expected progression of any underlying diseases or conditions of the participants
- The participant's pre-existing conditions and risk profile for the event

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an AE or SAE may come to the attention of study personnel from review of electronic medical record data or from a study participant contacting the patient navigator.

All AEs, not otherwise precluded per the protocol, will be captured on the appropriate CRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study procedures (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study will be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical or psychiatric condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. Documentation of onset and duration of each episode will be maintained for AEs characterized as intermittent.

The PI and/or project manager will record events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation.

8.3.5 ADVERSE EVENT REPORTING

The PI will report AEs that are determined to be unanticipated problems to the KPSC IRB within 10 business days of discovery and at the continuing review period.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

The PI will be responsible for conducting an evaluation of a SAE based on the unanticipated problem analysis and shall report the results of such evaluation to the NIH and the KPSC IRB as soon as possible, but no event later than 10 working days after the investigator first learns of the event. In the event of the death of a study participant, reporting will fall under one of the following pathways:

(1) Death of an intervention study participant + unanticipated problem determination – the PI will report to the Institutional Review Board within 1 business day of discovery and at continuing review
(2) Death of an intervention study participant + NOT an unanticipated problem – the PI will report at continuing review
(3) Death of a non-interventional study participant – the event is not reportable

8.3.7 REPORTING EVENTS TO PARTICIPANTS

N/A

8.3.8 EVENTS OF SPECIAL INTEREST

N/A

8.3.9 REPORTING OF PREGNANCY

N/A

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS

As per the definition provided by the KPSC IRB we will consider any AE under this protocol a reportable unanticipated problem (UP) if the event meets all three criteria:

- Unexpected in nature, severity, or frequency
- Related or possibly related to participation in the research
- Suggests greater risk to participants or others than previously known

Corrective actions or changes that may be considered in response to a UP are:

- Modification of inclusion or exclusion criteria to mitigate the newly identified risks
- Implementation of additional safety monitoring procedures
- Suspension of consenting/enrollment of new participants or halting of study procedures for consented/enrolled participants
- Modification of informed consent documents to include a description of newly recognized risks
- Provision of additional information about newly recognized risks to previously consented/enrolled participants

8.4.2 UNANTICIPATED PROBLEMS REPORTING

The PI will report UPs to the reviewing KPSC IRB. The UP report will include the following information:

- Protocol identifying information: protocol title and number, Principal Investigator's name, and the IRB project number
- A detailed description of the event, incident, experience, or outcome
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are SAEs will be reported to the IRB and the study funding agency within 10 business days of the investigator becoming aware of the event; within one day in the event of the death of a participant if determined a UP.
- Any other UP will be reported to the IRB and to the funding agency within 10 business days of the investigator becoming aware of the problem

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

N/A

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

As the UG3 phase focuses on adaptation of existing navigation programs, we do not have formal hypotheses for these aims.

9.2 SAMPLE SIZE DETERMINATION

Qualitative data collection does not require power analysis. The focus groups have a target sample size of 6-8 participants per group, as recommended as best practice.

The single-arm pilot study will target 15-25 patient participants with estimates based on a reasonable number of participants to test the adapted navigation methods (e.g., patient contacts, navigation goals) and to provide insights into their care experiences within the program via patient survey. Similarly, clinicians/administrators at the pilot study site will be asked to complete a survey on their experiences with the program. Power analyses are not appropriate for these aims.

9.3 POPULATIONS FOR ANALYSES

N/A

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

UG3 phase: Focus groups and surveys

Focus groups: Each group session will last approximately 1.5-2 hours and will be audio-recorded with an experienced notetaker present; recordings will be transcribed by a professional transcription vendor.

We will use NVivo qualitative software to guide the analysis. Using a team coding approach relying on multiple coders (e.g., 2-3 research staff with qualitative research experience), we will generate initial coding categories from the preliminary research questions to create a start list of codes. Using the constant comparative method, coders will independently review the transcripts, applying the start lists of codes to the text, as well as generating their own emergent coding categories and analytical memos We will incorporate the FRAME into the qualitative analyses to identify both processes and reasons for adaptation (e.g., who participated, goals, contextual adaptations).

Survey Data Collection and Analysis. We will collect demographic information (e.g., age, race, ethnicity, census-level education and income) and clinical information (e.g., date of cancer diagnosis, age at diagnosis, disease stage, cancer treatment type, tumor genomics) from the EMR and tumor registry for all participants. We will collect for clinician variables such as gender, race, and years in

practice from the EMR. Sex as a potentially important biologic factor will be included in all analyses. Use of existing data in the EMR can other databases is in alignment with the highly pragmatic nature of the trial.

We will create descriptive summary tables of results. We did not do a formal power analysis for the pilot data, as this will be only one clinic site and the purpose is to identify areas needing additional refinement prior to the launch of the pragmatic trial.

9.4.2 ANALYSIS OF THE PRIMARY ENDPOINT(S)

As described above.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

N/A

9.4.4 SAFETY ANALYSES

N/A

9.4.5 BASELINE DESCRIPTIVE STATISTICS

N/A

9.4.6 PLANNED INTERIM ANALYSES

N/A

9.4.7 SUB-GROUP ANALYSES

N/A

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

N/A

9.4.9 EXPLORATORY ANALYSES

N/A

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

For this study, a waiver of informed consent will be required to identify KPSC AYA cancer survivors by condition who are eligible for enrollment into the adapted PN program pilot study and inclusion in the focus group recruitment sample. We do not foresee any risks to potential participants by not directly consenting them to participate for identification by condition. This study poses minimal risk to AYA cancer survivors because survivorship cancer care will be performed as part of routine medical care that is consistent with guidelines from professional societies and organizations. The pilot adapted PN program will focus on directing enrolled AYA patients to guideline-recommended services that already exist, essentially bridging service gaps for this population. In addition, participation in the adapted PN program will be voluntary. We also believe that such a waiver of consent is not only widely recognized as necessary an appropriate, but also scientifically necessary and ethically justifiable under the "Common Rule" for protection of research participants (45 CFR 46.116d). We also requested a HIPAA authorization waiver for the identification of KSPC AYA cancer survivors for potential enrollment into the pilot adapted PN program and inclusion in the focus group recruitment sample. It will be prohibitive to contact patients directly for identification by condition and this study poses no more than minimal risk to privacy and confidentiality of study participants.

<u>For patient, clinician, and administrator focus groups and surveys</u>:

- For the UG3 phase patient focus groups, we will submit modifications to the KPSC IRB that include consenting and HIPAA procedures and forms before conducting the interviews. In addition, we will request a waiver of informed consent for the clinician and administrator focus groups.
- Should the UG3 phase of the study be successful and we receive funding for the UH3 trial phase, we will submit all necessary focus group and survey recruitment and consenting procedures, including patient-, clinician, and administrator-facing written consent forms/oral consent procedures, recruitment scripts, etc. to the KPSC IRB for approval. We will update this protocol at the time these forms and procedures are approved by the KPSC IRB.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Consent procedures and documentation for all patient, clinician, and administrator focus group and survey activities for the UG3 and UH3 phases of this study will be approved via future modifications to the KPSC IRB **PRIOR** to the conduct of any of these activities with participants. Updates to this protocol will

be made at the time we receive approval from the KPSC IRB for any modification requests related to consenting and documentation procedures for the focus group and survey activities.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency, and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the KPSC IRB, and sponsor/funding agency and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the funding agency, KPSC IRB, or other relevant regulatory or oversight bodies (OHRP, DSMB).]

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality will be maintained at all times. Each focus group and survey participant will be given a unique alpha-numeric identification number. No data collection form will be linked to an actual participant name. Any document linking the participant name to an identification number will be kept in a locked file separate from data collection files. All records from the study will be kept in locked files within the KPSC Department of Research and Evaluation. Identifying information will be removed from the final data sets and stored in a linked file to which only the Principal Investigator or designee(s) have access. Individual participants will not be identified in any reports. Additionally, study reports will be aggregated so that individual participants are not identified. Quotes from qualitative data will be reported using no name or identifying descriptors or will use pseudonyms. All investigators and research staff at participating sites will be required to maintain up-to-date training in human subject protection and good clinical practice through Collaborative Institutional Training Initiative (CITI; https://www.citiprogram.org) and HIPAA training. Additional security precautions include encryption, digital certification, audit logs, and firewall protection.

The study monitor, other authorized representatives of the sponsor or funding agency, or representatives of the KPSC IRB may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) for the participants in this study.

The clinical study site will permit access to such records. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the KPSC IRB.

Measures Taken to Ensure Confidentiality of Data Shared per the NIH Data Sharing Policies. The PI will ensure all mechanisms used to share data will include proper plans and safeguards for the protection of privacy, confidentiality, and security for data dissemination and reuse (e.g., all data will be thoroughly de-identified and will not be traceable to a specific study participant; see Section 10.1.4 for details). Plans for archiving and long-term preservation of the data will be implemented as appropriate. A Certificate of Confidentiality is not required for this study.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

We are committed to the open and timely dissemination of study data and research outcomes to the broader community of health care providers, investigators, patients, health care systems, and public health personnel. The investigators agree to abide by the principles for sharing research resources as described by the National Cancer Institute's Cancer Moonshot public access and data sharing policy. Publications based on the study will adhere to the NIH Public Access Policy. Study data will be de-identified and made available for use in subsequent studies by other investigators to the extent feasible, pursuant to details as outlined below.

The study will also produce deliverables that will be freely available to the cancer care community including protocols for the interventions as well as EMR algorithms (e.g., risk-stratification), and clinician and patient educational tools. We will engage in presentation and publication of findings, and have structured each Aim to have publishable results, with an expectation of multiple opportunities for scientific presentations and manuscripts.

Our plan to support efforts by other researchers to replicate this study in other oncology settings and practices, as well as for other healthcare systems that wish to test and/or implement the resulting products, includes: 1) sharing of a complete, detailed study protocol; 2) sharing of intervention tools developed during the study; and 3) sharing of de-identified datasets to the extent possible and in accordance with KSPC Department of Research and Evaluation policies for sharing data.* Each of these activities will ensure transparency as well as replication so that other researchers will be able to apply the same study procedures, measures and analytic approaches to similar or novel populations. Our sharing of de-identified data will allow researchers to consider additional or associated questions or as a basis for collecting new data using this study design.

**Qualitative Data: Only de-identified, anonymous, thematic qualitative data will be available with no PHI (e.g., may include anonymous quotations). EMR Data: Only de-identified aggregated or summarized data (i.e., tables, graphs, summary descriptions) will be available including self-report survey data with no PHI.*

Metadata, other relevant data, and associated documentation: Documentation to be made available to the research community will include: study protocol published on ClinicalTrials.gov; semi-structured interview guides developed for the focus groups and interviews (provided in portable document format); tables of ICD/CPT codes.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

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We will convene an AYA and Primary Care Survivorship Council consisting of our local Chiefs of Service for family and internal medicine for our 5 target Southern California medical service areas with the highest proportions of traditionally underserved populations. We will include our Regional Chief of Oncology and Regional Oncology Department Administrator, and representatives from the KPSC Complete Care program. We will also include our external advisors representing the lived AYA cancer survivor experience, AYA clinical programs, and working with underserved populations. We will recruit AYA cancer survivors from KPSC and from the Cactus Cancer Society to be representatives on the Council to provide feedback on the structure and development of the PN program. We will rely on stakeholder engagement strategies we have used in the past to ensure that our work is relevant and responsive. Collectively, we will develop a shared vision for a collaborative, team-based, patient-focused, system-enabled PN program for AYA patients diagnosed with cancer. At completion of the focus groups, the Council will be presented with the integrated findings and the draft PN program outline. The study team will create a PN program mock-up with the suggested adaptations and tailored components based on our qualitative data collection, PN program theory, and organizational resources. Council meetings will be held bimonthly with a highly structured approach including pre-session communication including brief polls and executive summaries of relevant scientific literature and program development progress, and in-meeting presentations on adaptation, followed by discussion and consensus measurement. Council recommendations will be integrated into the PN program for the study and communicated to KPSC leadership as appropriate for program investment, development, and scale up/sustainment.

10.1.6 SAFETY OVERSIGHT

The Data and Safety Monitoring Plan (DSMP) for this study includes monitoring recruitment procedures and potential adverse events resulting from data collection (observational data from clinical and administrative databases, qualitative data from focus groups and/or individual interviews, and survey data) and from the intervention. There are minimal physical, psychological, or other risks associated with the proposed research based on the Common Rule, 45 CFR 46.116d, because this study involves the use of routine care practices, no investigational drugs or devices, and poses little risk of physical or psychological harm to patients in either the patient navigation program or usual care.

Therefore, we have considered our options to provide an independent review for safety; namely, employing either a Safety Officer (SO) or DSMB. Given the generally low risk faced by participants in this study, we believe that this trial can be monitored by the PI in the role of SO and the KPSC Institutional Review Board IRB.

Monitoring the Progress of Trials and the Safety of Participants. Demographic information (e.g., age, race, ethnicity, census-level education and income) and clinical information (e.g., date of cancer diagnosis, age at diagnosis, disease stage, cancer treatment, endocrine therapy) will be collected from the electronic medical record (EMR) for all participants. We will collect primary care clinician variables such as clinician gender, race, and years in practice from the EMR.

For the future pragmatic trial (UH3), we will prospectively identify adolescent and young adult (AYA) cancer survivors across our participating clinics using our comprehensive pathology database, Co-Path, combined with a text-information extraction system (a process we have used successfully in the past to identify newly diagnosed and on-treatment cancer patients). We will identify the end of active treatment (surgery, chemotherapy, and/or radiation) using our treatment databases (e.g., Beacon chemotherapy, Mosaiq radiation) and EMR data. This will ensure that we identify appropriate AYA cancer survivors to be included in the study.

Collection of observation data from administrative and clinical databases, self-reported demographics from the surveys, and intervention activities at the KPSC medical centers will be collected by the study programmer and/or statistician and discussed at weekly project meetings with the PI. During monthly investigator meetings, data and recruitment summary reports of demographic and clinical information will be presented. We will review utilization of services to assess for potential harm to the intervention participants, including examining time to detection of cancer recurrence which will be identified using validated algorithms for clinical data. Recruitment strategies for the surveys will be brainstormed for optimization as needed to address discrepancies in response by age, gender, and race/ethnicity. Recruitment success by racial/ethnic categories will be monitored closely and reported in NIH progress reports and to the SO/DSMB no less than annually.

Participant confidentiality. A Certificate of Confidentiality is not needed. IRB mandated procedures for the protection of confidentiality of subject data will be carefully followed. We will use medical record numbers to link individual-level data across clinical and administrative databases, and these medical record numbers will be replaced with unique study identifiers once these linkages are made. Survey participants will be given a unique alpha-numeric identification number that will be retained for all data collection forms. All data will be stored on secured shared drives accessed only using password-protected computers. We will minimize emailing patient data among project team members at KPSC; no patient identifying information from KPSC will be sent outside KPSC. Furthermore, study team members and clinicians will only use KPSC email accounts to send encrypted emails, ensuring that the sender and the recipient can verify the identity of the sender and/or recipient. In addition, confidentiality will be a topic of discussion in the meetings between investigators and research staff, as well as across collaborating medical centers.

Plans for assuring compliance with requirements regarding the identification and reporting of adverse events (AE) and unanticipated problems (UP) are outlined in **Sections 8.3-8.4**.

10.1.7 CLINICAL MONITORING

N/A

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Quality control (QC) procedures will be implemented as follows:

Informed consent

- Aim 1: See consent procedures for focus groups; we will request a waiver of documented informed consent (but use of a study information sheet) and HIPAA for the focus groups.
- Aim 2: We will request a waiver of documented informed consent (but use of a study information sheet) for the pilot study and associated surveys.

Source documents and the electronic data --- Data for this study are obtained from clinical and administrative databases and participant self-report for the surveys.

Intervention Fidelity — We will assess compliance with the study protocol monthly, with review of relevant data. We will collect utilization of navigation services for the pilot study. Clinical EMR data on utilization has a high degree of accuracy but will be reviewed at regular intervals to ensure quality and accuracy (e.g., chart review of outliers). Interim data checks will be done in aggregate, with means, median, and range checks performed quarterly.

Protocol Deviations – Throughout the study phases, we will work closely with our Institutional Review Board, clinical chiefs, and operational leaders to ensure patient safety, with regular review and reporting of adverse events and protocol deviations.

Should independent monitoring become necessary, the PI will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor/funding agency, and inspection by local and regulatory authorities.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Demographic and clinical information will be collected from the EMR for all participants by study programmers under the oversight of the PI. Self-reported demographics will be collected from those who participate in the surveys. Transcripts of interviews will be collected from those who participate in the focus groups. We will collect clinician variables such as clinician gender, race, and years in practice from the EMR. Clinical EMR data on utilization will be reviewed at regular intervals to ensure quality and accuracy (e.g., chart review of outliers). Interim data checks will be done in aggregate, with means, median, and range checks performed quarterly. All investigators and research staff at participating sites will be required to maintain up-to-date training in human subject protection and good clinical practice through Collaborative Institutional Training Initiative (CITI; https://www.citiprogram.org) and Health Insurance Portability and Accountability Act (HIPAA) training. Additional security precautions include encryption, digital certification, audit logs, and firewall protection.

10.1.9.2 STUDY RECORDS RETENTION

Study documents will be retained for a minimum of 2 years after cessation of study analyses. These documents should be retained for a longer period, however, if required by local regulations or additional studies using these data and resources.

10.1.10 PROTOCOL DEVIATIONS

This protocol uses the KPSC definition of protocol deviation: a protocol deviation is a departure from the IRB approved research plan that – a) does not place the safety, rights, or welfare of one or more study participants at risk AND b) does not impact the integrity of the study. As a result of deviations, corrective actions will be developed by the site and implemented promptly.

It will be the responsibility of the PI to use continuous vigilance to identify and report deviations at the next continuing review period of identification of the protocol deviation. All deviations will be addressed in study source documents, reported to the KPSC IRB for review per their policies. The site investigator will be responsible for knowing and adhering to the KPSC IRB requirements.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers up to 5 years after the completion of the primary endpoint by contacting the PI. Considerations for ensuring confidentiality of these shared data are described in **Sections 10.1.3 and 10.1.4**.

Details of data sharing include but are not limited to:

(1) Sharing of a complete, detailed study protocol and publications

We will ensure our study protocol is registered on ClinialTrials.gov prior to initiation of enrollment procedures. At the end of the study, we will provide an updated, detailed study protocol describing all

aspects of the study including the following: a) description of the study population, risk-stratification, sampling methods and resulting study sample; b) study design; recruitment and enrollment procedures; and primary care intervention components and implementation; c) data collection including programming algorithms to extract CPT-based utilization data; and d) copies of survey measures and data collection schedules and procedures. Our grant application becomes the initial draft of this protocol. This protocol will be updated at the end of the study planning phase to ensure that it provides a concrete, detailed, and specific step-by-step manual to allow replication. For reproducibility and for full transparency, any code or tools developed will be published along with the manuscript either through the journal website and/or GitHub or Open Science Framework website, which is hosted by the Center for Open Science (funded in part by the NIH and the National Science foundation) and is open to the public. We will also seek to publish this protocol in a relevant scientific journal. This and other publications generated from this study will:

(1) Be deposited in PubMed Central with proper tagging of metadata after acceptance by a journal;
(2) Will be published under the Creative Commons Attribution 4.0 Generic License or an equivalent license, or otherwise dedicated to the public domain;
(3) To the extent feasible, underlying primary data will be shared simultaneously with the publication.

2. Sharing of de-identified data for replication and additional studies

For this study, the Investigators will provide these research data in a controlled manner to outside researchers who are willing to enter into formal research relationships to ensure that the data will be used for scientific purposes in the public interest, that patient privacy will be protected, and that all other risks to participants will be minimized. All such requests will be reviewed by the Investigators for scientific merit, human subjects considerations, and KPSC legal obligations. Primary data will reside locally within the Kaiser Permanente Department of Research and Evaluation. After approval of the request, a data sharing agreement will be created, approved, and signed. Conditions may be placed on the use of the data, including but not limited to, no distribution to third parties, a KPSC researcher included on the study team, proper acknowledgement and citation of the data providers (as indicated in the data sharing agreement) and the NIH grant funding, exclusive use by the data recipient in connection with a specific research project, for which the recipient has sole responsibility and which is explicitly described, and agreement not to use the data in any effort to establish the identity of the study subjects. The data recipient will be subject to applicable federal, state, and local laws or regulations and institutional policies providing additional protections for human subjects.

De-identification of data: In order to protect the privacy rights of participants and confidentiality of their data, we will de-identify all data according to the standards set forth in the Health and Human Services Regulations for the Protection of Human Subjects; primary data will also be stripped of identifiers according to the HIPAA Privacy Rule. With input from the KPSC IRB, we will assess consent materials to determine whether data may be shared as contemplated in this policy.

If de-identified data can be shared, the following process and procedures is to be followed:

1. Requests will be evaluated individually by the PI of this study in conjunction with the Senior Director of Research and/or the Executive Committee of the Department of Research and Evaluation.
    a. Requests must be from a qualified, doctorate-level researcher;

   b. Requests must have a stated, achievable purpose and detailed plan that is of value to the clinical and/or research community.
2. A data use agreement and/or data transfer agreement must be executed for all requests. This must include:
   a. What data elements are to be included;
   b. How the data will be used;
   c. Details of any subsequent disclosure and prohibition of additional disclosure without an amendment;
   d. How long the data can be used;
   e. What will happen to the data when the project is complete
   f. Opportunity for review and comment.
3. De-identified datasets to be made available under this Plan must:
   a. Follow the definitions of de-identification as outlined by Health and Human Services Regulations for the Protection of Human Subjects and the HIPAA Privacy Rule;
   b. Use relative dates and round birth dates/ages;
   c. De-identify entity/site of care to be to the extent possible;
   d. Only include data to support publication.
4. An approval process will be in place, with required approvals from:
   a. SCPMG practice leader (typically Regional Chief of relevant specialty)
   b. SCPMG Area Medical Director
   c. Senior Director of Research, Department of Research and Evaluation
5. There will be no associated fees.

10.1.12 CONFLICT OF INTEREST POLICY

Any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with NCI has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ADDITIONAL CONSIDERATIONS

N/A

10.3 ABBREVIATIONS AND SPECIAL TERMS

AE	Adverse Event
AHRQ	Agency for Healthcare Research and Quality
ASCO	American Society of Clinical Oncology
AYA	Adolescent and Young Adult
COC	Certificate of Confidentiality
CRF	Case Report Form

DAs	Department Administrators
DSMB	Data Safety Monitoring Board
DSMP	Data Safety Monitoring Plan
EMR	Electronic Medical Record
FRAME	Focus, Reach, Ask, Model, and Encourage
HIPAA	Health Insurance Portability and Accountability Act
IRB	Institutional Review Board
IT	Information Technology
KPSC	Kaiser Permanente Southern California
MD	Medical Doctor
MEPS	Medical Expenditure Panel Survey
NAM	National Academy of Medicine
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NIH	National Institutes of Health
PHI	Protected Health Information
PN	Patient Navigator or Patient Navigation
PO	Project Officer
POE	Proactive Office Encounter
PRECIS-2	Pragmatic-Explanatory Continuum Indicator Summary-2
PI	Principal Investigator
RE-AIM	Reach, Effectiveness, Adoption, Implementation and Maintenance
REDcap	Research Electronic Data Capture
SAE	Serious Adverse Event
SO	Safety Officer
UP	Unanticipated Problem
US	United States
USPSTF	U.S. Preventive Services Task Force

10.4 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale
1.0	1/27/2026	N/A; First Version	

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