The Engaging Primary Care in Cancer Survivorship (EPICS) study*

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Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale
Face Page	1. Updated protocol number; version number and date from 2.0 to 3.0	1. Protocol number updated to reflect amendment
1.1 Synopsis; 1.3 Schedule of Activities; 2.1 Study Rationale; 5.5 Strategies for Recruitment-Retention; 9/2 Sample Size Determination	1. Changed the number of anticipated participants to a minimum of 2450	1. Based on updated analysis plan
1.2 Schema	1. Inserted new schema figure	1. Based on updated anticipated accrual
1.3 Schedule of Activities	1. Extended to Year 3, Quarter 4 for patient recruitment	1. Recruitment activities were halted Winter 2021 due to COVID surges
5.1 Inclusion Criteria	1. Lengthened patient eligibility window from 6-18 months to 6-36 months from treatment end date	1. Fewer patients than anticipated were diagnosed with early stage breast or colorectal cancer in 2020-2021, due to cessation of screening activities and slow return-to-screening required by the COVID pandemic
9.2 Sample Size Determination	1. Updated justification for sample size and analysis plan for Aims 1 and 2	1. Based on need to update anticipated accrual due to impacts from the COVID pandemic
9.4 Statistical Analysis; 9.4.1 General Approach; 9.4.2 Analysis of the Primary Endpoint(s); 9.4.3 Analysis of the Secondary Endpoint(s)	1. Updated statistical analysis plan for Aims 1-3	1. Based on need to update anticipated accrual due to impacts from the COVID pandemic

CONFIDENTIALITY STATEMENT

Table of Contents

STATEMENT OF COMPLIANCE 1
INVESTIGATOR'S SIGNATURE 2
1 PROTOCOL SUMMARY 3
1.1 Synopsis 3
1.2 Schema 5
1.3 Schedule of Activities 6
2 INTRODUCTION 7
2.1 Study Rationale 7
2.2 Risk/Benefit Assessment 9
2.2.1 Known Potential Risks 9
2.2.2 Known Potential Benefits 10
2.2.3 Assessment of Potential Risks and Benefits 10
3 OBJECTIVES AND ENDPOINTS 11
4 STUDY DESIGN 12
4.1 Overall Design 12
4.2 Scientific Rationale for Study Design 15
4.3 Justification for Intervention 15
4.4 End-of-Study Definition 16
5 STUDY POPULATION 16
5.1 Inclusion Criteria 16
5.2 Exclusion Criteria 17
5.3 Lifestyle Considerations 17
5.4 Screen Failures 17
5.5 Strategies for Recruitment and Retention 18
6 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S) 20
6.1 Study Intervention(s) or Experimental Manipulation(s) Administration 20
6.1.1 Study Intervention or Experimental Manipulation Description 20
6.1.2 Administration and/or Dosing 21
6.2 Fidelity 23
6.2.1 Interventionist Training and Tracking 23
6.3 Measures to Minimize Bias: Randomization and Blinding 23
6.4 Study Intervention/Experimental Manipulation Adherence 23
6.5 Concomitant Therapy 23
6.5.1 Rescue Therapy 23
7 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL 23
7.1 Discontinuation of Study Intervention/Experimental Manipulation 23
7.2 Participant Discontinuation/Withdrawal from the Study 24
7.3 Lost to Follow-Up 24
8 STUDY ASSESSMENTS AND PROCEDURES 25
8.1 Endpoint and Other Non-Safety Assessments 25
8.2 Safety Assessments 27
8.3 Adverse Events and Serious Adverse Events 27
8.3.1 Definition of Adverse Events 27
8.3.2 Definition of Serious Adverse Events 28

8.3.3 Classification of an Adverse Event 28
8.3.4 Time Period and Frequency for Event Assessment and Follow-Up 29
8.3.5 Adverse Event Reporting 30
8.3.6 Serious Adverse Event Reporting 30
8.3.7 Reporting Events to Participants 30
8.3.8 Events of Special Interest 30
8.3.9 Reporting of Pregnancy 30
8.4 Unanticipated Problems 31
8.4.1 Definition of Unanticipated Problems 31
8.4.2 Unanticipated Problems Reporting 31
8.4.3 Reporting Unanticipated Problems to Participants 32
9 STATISTICAL CONSIDERATIONS 32
9.1 Statistical Hypotheses 32
9.2 Sample Size Determination 32
9.3 Populations for Analyses 36
9.4 Statistical Analyses 36
9.4.1 General Approach 36
9.4.2 Analysis of the Primary Endpoint(s) 36
9.4.3 Analysis of the Secondary Endpoint(s) 37
9.4.4 Safety Analyses 38
9.4.5 Baseline Descriptive Statistics 38
9.4.6 Planned Interim Analyses 38
9.4.7 Sub-Group Analyses 38
9.4.8 Tabulation of Individual Participant Data 38
9.4.9 Exploratory Analyses 39
10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS 39
10.1 Regulatory, Ethical, and Study Oversight Considerations 39
10.1.1 Informed Consent Process 39
10.1.2 Study Discontinuation and Closure 40
10.1.3 Confidentiality and Privacy 40
10.1.4 Future Use of Stored Specimens and Data 41
10.1.5 Key Roles and Study Governance 41
10.1.6 Safety Oversight 42
10.1.7 Clinical Monitoring 42
10.1.8 Quality Assurance and Quality Control 42
10.1.9 Data Handling and Record Keeping 43
10.1.10 Protocol Deviations 44
10.1.11 Publication and Data Sharing Policy 44
10.1.12 Conflict of Interest Policy 46
10.2 Additional Considerations 47
10.3 Abbreviations and Special Terms 47
10.4 Protocol Amendment History 48
11 REFERENCES 50

STATEMENT OF COMPLIANCE

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.

Principal Investigator or Clinical Site Investigator:

Signed: _____ Date: _____

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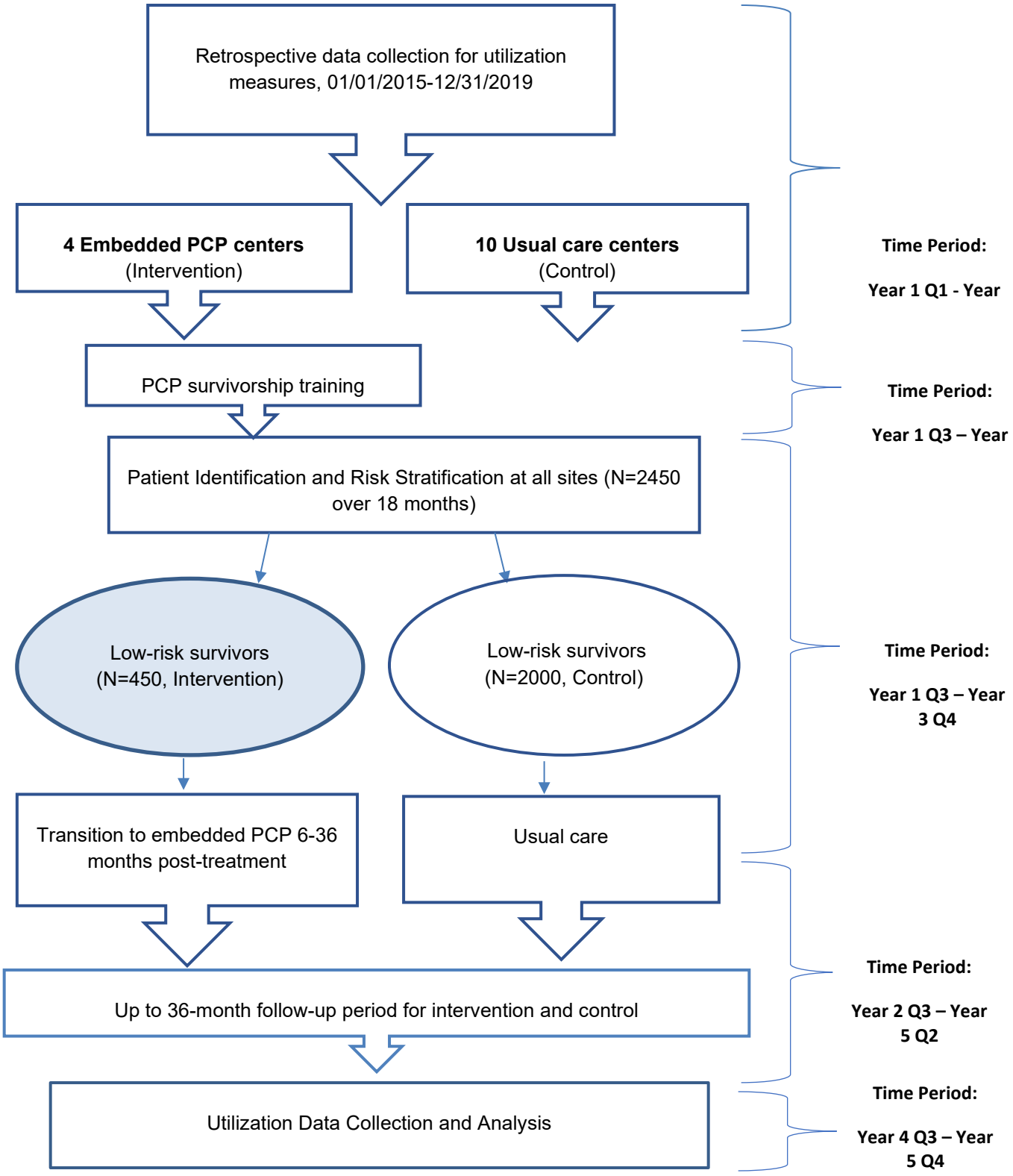
1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	The Engaging Primary Care in Cancer Survivorship (EPICS) study
Grant Number:	1R01CA249419-01
Study Description:	This is a quasi-experimental pre/post with control group trial of two models of cancer survivorship care in early-stage colorectal and breast cancer survivors cared for in a community-based, integrated health care setting. The trial will test the efficacy of an embedded primary care provider (PCP) model (experimental condition) in which survivorship-trained PCPs are embedded within an oncology practice to care for low-risk survivors who will be transitioned at 6-36 months post-treatment for comprehensive survivorship care. We hypothesize that a) patients in the PCP model will have superior receipt of recommended care compared to usual care; b) patients in the PCP model will perceive significantly better care coordination, self-efficacy, and confidence in their PCP compared to usual care; and c) use of unplanned and non-recommended care will be less in the PCP model compared to usual care.
Objectives*:	Primary Objective: To determine the efficacy of an embedded PCP model (experimental condition) compared to usual care on use of recommended cancer surveillance and preventive care services. Secondary Objectives: 1) To determine the efficacy of an embedded PCP model (experimental condition) compared to usual care on patient-reported outcomes; 2) to compare use of unplanned and non-recommended care in the PCP model compared to usual care.
Endpoints*:	Primary Endpoint: Receipt of guideline-recommended cancer surveillance and preventive care services assessed over a 36-month period. Secondary Endpoints: 1) Patient reported outcomes: Validated measures of patient and provider communication, and coordination of survivorship care; important covariates will include quality of life, physical and mental health, assessment of survivorship care delivery, and satisfaction with health decisions; 2) Receipt of non-recommended surveillance care based on current clinical guidelines, and use of non-planned hospitalization, emergency department, and urgent care services.

Study Population:	Patients: Adult (21+) Kaiser Permanente Southern California members diagnosed and treated for first primary early-stage breast (stage 0, I, II) or colorectal (stage I, II) cancer within Kaiser Permanente Southern California. Patients will be at low-risk for recurrence and treatment-related toxicities, as determined by our risk algorithm. Physicians: For centers in the embedded PCP model, PCPs selected to participate must be Board Certified in a relevant primary care specialty; hold a valid and current MD or advanced practitioner license; and be employed by the Southern California Permanente Medical Group.
Phase* or Stage:	This is a single site phase III National Institutes of Health Clinical Trial
Description of Sites/Facilities Enrolling Participants:	This trial will be conducted in a community-based integrated system, Kaiser Permanente Southern California (KPSC). KPSC medical oncology departments in the intervention group will enroll eligible patients into the intervention. KPSC oncology departments in the control group will passively enroll patients for tracking of utilization.
Description of Study Intervention/Experimental Manipulation:	Embedded PCPs will provide comprehensive care for eligible survivors at intervention sites, including cancer surveillance services, preventive care, and management of long-term therapy and associated side effects (e.g., endocrine therapy in breast survivors). A comprehensive multilevel approach will prepare survivors and PCPs. Intervention: Embedded PCP. Embedded PCPs will be enrolled in a 4-month course of initial training and education, followed by ongoing education via tailored survivorship information for low-risk survivors transitioning to their care. Initial training features 3 core components to build capacity, skill, and knowledge: 1) Individual didactic learning; 2) Small in-person group sessions; and 3) Observation. Intervention: Patient-level. Eligible patients in the embedded PCP model will be provided with tailored education regarding the planned transition prior to the transition. After cessation of active treatment, the care team will provide printed information including the planned course of survivorship care, what to expect from embedded PCP care, when the transition will occur, and reassurance that the oncology team will be available via telephone and email, and that PCPs will refer back to the oncologist for any concerning signs or symptoms. Intervention: System-level. Tailored alerts in the electronic medical record for recommended cancer surveillance and preventive care services that include rationale, links to guidelines, and references for questions (scheduled to fire when survivors have an outpatient office visit with their embedded PCP, following the same rationale for the alerts to fire during oncology visits).
Study Duration*:	60-months
Participant Duration:	36-months

1.2 SCHEMA


Retrospective data collection for utilization measures, 01/01/2015-12/31/2019
4 Embedded PCP centers (Intervention)
10 Usual care centers (Control)
PCP survivorship training
Patient Identification and Risk Stratification at all sites (N=2450 over 18 months)
Low-risk survivors (N=450, Intervention)
Low-risk survivors (N=2000, Control)
Transition to embedded PCP 6-36 months post-treatment
Usual care
Up to 36-month follow-up period for intervention and control
Utilization Data Collection and Analysis
Time Period: Year 1 Q1 - Year
Time Period: Year 1 Q3 – Year
Time Period: Year 1 Q3 – Year 3 Q4
Time Period: Year 2 Q3 – Year 5 Q2
Time Period: Year 4 Q3 – Year 5 Q4

1.3 SCHEDULE OF ACTIVITIES

	Year 1				Year 2				Year 3				Year 4				Year 5			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Administrative and regulatory tasks	X	X																		
Center assignment		X	X																	
Pre-period data collection and analysis			X	X	X	X														
Initiate primary care training at intervention sites			X	X	X															
Annual PCP survey of knowledge, confidence in survivorship care					X				X				X				X			
Patient identification, risk stratification at all sites			X	X	X	X	X													
Enrollment period into intervention or usual care, N=2450						X	X	X	X	X	X	X								
Follow-up period for intervention or usual care (up to 36 months)							X	X	X	X	X	X	X	X	X	X	X	X		
Patient survey at 12 months post-transition (rolling recruitment)										X	X	X	X	X						
Survey analyses (Aim 2)															X	X	X			
Refine EMR-based measures of utilization																X	X			
Obtain EMR data on utilization, initiate analyses (Aims 1, 3)																		X	X	X

2 INTRODUCTION

2.1 STUDY RATIONALE

Advances in treatment and detection of cancer have led to a rapidly growing population of cancer survivors. Significant growth of cancer patients, particularly those ≥65 years, is predicted within the U.S over the next 20 years.[1] The majority of these patients will enter into a prolonged post-treatment phase of care and considered cancer survivors.[2] *Cancer survivor* is commonly defined as from the time of diagnosis through the balance of his or her life, as originally articulated by the National Coalition for Cancer Survivorship.[3] For this proposal, we are focusing on the transition from the end of active cancer treatment (e.g., surgery, chemotherapy, radiation) to the post-treatment survivorship phase, which may include extended hormonal or other chronic therapy. Survivors require coordinated, comprehensive care addressing the major domains of survivorship as described by National Academy of Medicine, the American Society for Clinical Oncology (ASCO) and others, including surveillance for recurrence, screening for new cancers, screening and management for long-term and late effects, symptom management, and preventive care (e.g., vaccinations, screening for other diseases).[4-13] Older survivors (>65 years), who make up the majority of cancer survivors, also have a higher prevalence of comorbid conditions requiring management and coordination of care.[1]

We are facing unprecedented challenges in survivorship care delivery. Currently, survivorship care delivery is unsystematic, occurs in a variety of settings, and is often poorly coordinated.[14-16] Serious gaps in survivorship care have been identified, including underuse of guideline-recommended cancer surveillance services, such as annual mammography for breast cancer survivors and colonoscopy for colorectal cancer (CRC) survivors,[17-22] and underuse of recommended preventive care services such as vaccinations, lipid testing and cardiovascular risk management, and cancer screenings.[23-27] In addition, the frequent overuse of non-recommended services that provide limited benefit exposes patients to significant harms, as exemplified by use of non-recommended serum tumor marker tests and high-intensity imaging for surveillance of early stage CRC and breast cancer.[17, 28-36] Breast and CRC survivors have characterized their survivorship care as lacking in information for follow-up and providing inadequate support to address their needs.[37] Compounding these issues, our current oncology workforce is insufficient to care for the rapidly growing population of survivors.[1, 38, 39] Estimates from ASCO show a projected growth in demand of approximately 50% and only 14% growth in clinician supply, with demand exceeding supply as soon as 2020.[40, 41] This demand is increasing wait times for oncology services across the U.S.[42] The current approach to delivering survivorship care, which is typically with oncology specialists with limited or no coordination with primary care, is inadequate and fails to meet the needs of many survivors.[6] In this study, we will evaluate a new approach to survivorship care that embeds survivorship-trained primary care providers (PCPs) into the oncology setting to provide survivorship care for low-risk survivors, potentially alleviating demand for oncology services while maintaining quality care.

PCP-led survivorship care is feasible, but critical barriers must be addressed. In observational studies, survivors who receive care that involves PCPs (whether physicians or advance practice providers) received

higher quality of care. [23, 25, 43-46] Most survivors expect PCPs to manage their general preventive care.[47] PCPs are well-positioned to counsel survivors regarding lifestyle choices such as physical activity,[48] disease prevention,[49] screening for psychosocial health needs,[50] and tobacco cessation.[51] Receipt of CVD preventive care in cancer survivors was strongly associated with PCP involvement.[52] PCPs receive high ratings on care coordination and comprehensive care during survivorship.[53] However, lack of knowledge and other barriers must be addressed for PCPs to assume primary responsibility for survivorship care; for example, a recent survey of PCPs found that less than half of guideline-recommended services for breast cancer survivors were routinely used.[54] Additionally, survivors may not be comfortable transitioning to a PCP for survivorship.[55, 56] Some survivors may prefer oncology-led cancer surveillance based on emotional reasons and feeling connected to their oncology team.[57, 58] Other barriers perceived by clinicians and survivors include poor communication with oncology,[59] lack of knowledge regarding existing guidelines,[60] limitations of health information technology and support,[61] and inadequate survivorship training and education.[58, 60, 62-66] Survivorship care plans (SCPs), summative documents intended to help improve communication and coordination of survivorship care,[7] may be a necessary but insufficient tool to address these issues. SCPs have been shown to help PCPs feel more prepared and knowledgeable about survivorship care delivery,[67] improve PCP-reported care coordination and communication,[68] and may improve quality of survivorship care[69-71] and patient self-efficacy.[72] However, results from most randomized controlled trials (RCTs) have found little to no effect of SCPs on distress, quality of life, or satisfaction with care.[73, 74] Thus, SCPs alone may be a necessary but insufficient component to engage PCPs and improve quality of survivorship care.[73, 75-77] We will address these barriers identified in the empirical literature in our study with multi-level interventions (patient, provider, system) incorporating robust education, training, and support for survivorship care.

The need for risk-stratified survivorship care. Risk-stratified survivorship care has been suggested as a potential model for U.S. survivors.[10, 41, 78-80] Risk-stratification involves evaluation of cancer and treatment characteristics, risk of complications, comorbid conditions, and other patient characteristics. In this approach, survivors with less complicated cancer treatments and at low-risk for recurrence or treatment toxicities are triaged to a less intense pathway (e.g., PCP-led or self-management) and patients with more complex cancer treatments/stage of disease are triaged to specialist oncology care for ongoing follow-up.[41, 80] This type of stratification has been implemented within the National Health Service in the U.K.,[81-83] and a similar approach has been implemented in Northern Ireland.[84] Recent data show successful triage of half of CRC survivors and approximately 80% of breast survivors to a low-intensity survivorship pathway.[82] In the U.K. the stratified pathways have been found to improve access to oncology specialists and are projected to save approximately £90 million over 5 years.[80] We will integrate a risk-stratified approach in our study to identify and triage low-risk CRC and breast cancer survivors, incorporating these evidence-based recommendations.

To address these issues, we will conduct a pre/post with control trial of two models of cancer survivorship care in early-stage colorectal and breast cancer survivors cared for in a community-based, integrated health care setting. Building on our pilot work[57] and drawing on the empirical literature, we will test the efficacy of an embedded PCP model (experimental condition) in which PCPs are embedded within an

oncology practice, and will care for low-risk survivors who will be transitioned approximately 6-36 months post-treatment for comprehensive survivorship care. These PCPs will be given training in cancer survivorship care focused on cancer surveillance and chronic disease prevention. This model will be compared to the extant oncology physician model (usual care) that is the default condition in the health care system. The primary outcome will be receipt of guideline-recommended care (e.g., cancer surveillance, preventive care), assessed over a 36-month period. Secondary outcomes will include validated patient-reported outcomes (PROs), as well as utilization of unplanned care (hospitalizations, urgent care) and receipt of non-recommended care. We will also explore PCP perceptions of confidence in delivery of survivorship care. We will conduct this trial in large medical centers of an integrated health care system, Kaiser Permanente Southern California (KPSC), with approximately 2450 survivors. Data from multiple studies conducted by our team demonstrate the need to improve survivorship care in this setting[31, 32] and our recent pilot study demonstrates the feasibility of the embedded PCP model in this setting.[57] KPSC is an exceptional setting to conduct the proposed research with unparalleled access to longitudinal data, a large and diverse patient population, and engaged clinicians.

2.2 RISK/BENEFIT ASSESSMENT

2.2.1 KNOWN POTENTIAL RISKS

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 Aims 1 or 3, thus there is minimal risk to loss of privacy or confidentiality; demographic, clinical and utilization data for these Aims will be collected from EMR and/or claims data with no participant interaction. Data on potential adverse events and serious adverse events will be collected and reported to our Data Safety and Monitoring Board as described in Section 8.2 below.

For this study, a waiver for informed consent will be required to ensure a scientifically valid comparison of the embedded PCP (ePCP) model to current usual care.

We do not foresee any risks to potential participants by not directly consenting them to participate in the trial. This study poses minimal risk to the patient because survivorship cancer care will be performed as part of routine medical care, and both the ePCP and the oncology-based model for survivorship cancer care are consistent with guidelines from professional societies and organizations with regard to the delivery of safe, appropriate, and usual care practices. 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 or 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, clinical chiefs, and operational leaders to ensure patient safety, with regular review and reporting of adverse events and protocol deviations.

Patients will be individually recruited for patient-reported outcome surveys under Aim 2, initially through email and subsequently through mail and telephone. If email addresses are unavailable, we will use mailed letters as the initial contact. Recruitment scripts will describe the purpose of the research, the selection process for participation, the study structure and time commitment (one-time survey), and risks of participating. We will obtain written or oral consent from all participants for participation in the surveys. Survey consents and opt out options will be built into an electronic template as part of the initial survey screens.

For utilization data captured under Aim 3 from the EMR, individual patients will not be recruited and the ethical justification of the waiver of individual consent, the "Common Rule" for protection of research participants (45 CFR 46.116d), is outlined above.

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 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. Identifying information will be removed from the final data sets and stored in a linked file to which only the Principal Investigator 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://www.citiprogram.org/default.asp) and HIPAA training. Additional security precautions include encryption, digital certification, audit logs, and firewall protection.

2.2.2 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 trials in the U.S. comparing two survivorship models of care and one of the first to use a novel risk-stratified approach that will triage low-risk breast cancer and CRC survivors to one of these models of care. In addition, the study uses a multi-level approach that includes patient-, provider- and system-level components. Furthermore, the ePCP training materials and resources that will comprise a study "toolkit" are mostly free, widely-accessible materials and our risk-stratification methods are easily replicable, making our findings from this study well-poised for scale-up and dissemination.

2.2.3 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 Aims 1 or 3, thus there is minimal risk to loss of privacy or confidentiality; demographic, clinical and utilization data for these Aims 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 outlines in section 2.31 above.

This research is essential to advance the field of survivorship cancer care. Definitive evidence on effective models of care that engage primary care physicians and patients in survivorship with equivalent or superior outcomes to oncology-led models would allow clinicians, health system leaders, and policy makers to widely and confidently implement a new approach to survivorship that optimizes patient outcomes and efficiently employs resources.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To determine the efficacy of an ePCP model (experimental condition) compared to usual care on use of recommended cancer surveillance and preventive care services.	Receipt of guideline-recommended cancer surveillance and preventive care services assessed over a 36-month period	ePCPs trained to provide care to cancer survivors will provide superior care for preventive services and equivalent cancer surveillance care compared to the usual care model.
Secondary		
To determine the efficacy of an ePCP model (experimental condition) compared to usual care on patient-reported outcomes.	Validated, reliable measures of patient-provider communication, and coordination of survivorship care. We will include quality of life, physical and mental health, assessment of survivorship care delivery, and satisfaction with	ePCPs trained to provide care to cancer survivors will have superior communication and care coordination compared to usual care.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
	health decisions as important covariates.	
To determine the efficacy of an ePCP model (experimental condition) compared to usual care on utilization of emergency, urgent, hospital, and non-recommended care.	Utilization: Unplanned care (hospitalizations, emergency department, and urgent care); and receipt of non-recommended cancer surveillance care as described by clinical practice guidelines (e.g., ASCO Choosing Wisely)	ePCPs trained to provide care to cancer survivors may have different rates of patients with unplanned care or non-recommended care.
Tertiary/Exploratory		
To explore knowledge and confidence in survivorship care between ePCPs and PCPs at usual care centers.	Confidence in delivery of survivorship care and knowledge of survivorship care guidelines, assesses using validated survey questions.	Causal mechanism: ePCPs exposed to our multi-level intervention of education, training, and support will demonstrate superior knowledge and confidence in delivery of survivorship care compared to PCPs at the usual care centers, who are not exposed.

4 STUDY DESIGN

4.1 OVERALL DESIGN

Our study was originally designed as a cluster randomized trial of two models of cancer survivorship care. However, as a result of the SARS-CoV-2 pandemic (COVID) and the overwhelming clinical demands experienced by out study sites from multiple COVID surges, we re-designed our study from a cluster randomized trial to a quasi-experimental pre/post with control group design. This design allows us to meet our originally proposed aims and scop*e.*

As a result of the pandemic and the overwhelming COVID surges in the Southern California region, Kaiser Permanente Southern California (KPSC) clinical and administrative staff and facilities entered into 'surge' mode. Surge plans, which are prepared to cope with emergencies such as this pandemic, re-deploy clinical and administrative staff as needed to new positions and assess and redistribute/close medical facilities. During the initial 6 months of the pandemic, many KPSC medical office buildings were closed or had limited services and primary care physicians were re-deployed as hospitalists, ICU relief staff, and as virtual care consultants. Nursing teams from both primary care and oncology were re-deployed into hospital care, urgent care, virtual care, and into new roles such as COVID education and COVID testing. This had a serious impact on our study as medical centers that had committed to participate in our originally proposed design were no longer confident that they had the primary care resources and staff to participate, as our study requires significant clinical time from primary care for training and patient care. Several of our centers informed us they could only participate if they could be assigned to the control condition.

To address these extraordinary circumstances, and to preserve our ability to meet our study aims and scope, we re-designed our study from a cluster randomized trial to a quasi-experimental pre/post with control group design. As we no longer have the element of randomization, we have increased the number of participating medical centers from 8 to 14 (4 intervention, 10 control). This increases our projected number of prospective patient participants from 2,000 to an estimated minimum of 2,450. We have also added a 'pre' data collection period to collect retrospective patient utilization data from all participating centers to allow for comparison of pre-intervention and post-intervention outcomes (Aims 1 and 3). Additionally, to address the potential differences between our intervention and control sites, we have fielded a brief survey to all center Medical Directors about the impact of COVID and other factors that may have contributed to their decision/ability to participate in the study. We are also collecting data on clinician, patient, and geographic factors. This adaptation to the study design was approved via telephone discussion by our program officer at the National Cancer Institute in accordance with NIH Grants Policy Statement, 8.1.2 on October 5, 2020.

Updated Design. This is a single site (KPSC), multi-center (multiple KPSC medical centers) trial using a non-randomized pre/post control group design to compare the effectiveness of 2 risk-stratified models of survivorship care, an ePCP model with a survivorship-trained PCP providing cancer surveillance, symptom management, and preventive care, compared to an oncology-led model, where the survivor stays with their oncology team (usual care within the KPSC system). We will address the barriers to PCP involvement from the empirical literature and propose to measure recommended quality outcomes including receipt of recommended care, PROs, and utilization of hospital, urgent, and non-recommended care.

This trial will evaluate the efficacy of 2 models of cancer survivorship care on receipt of recommended care for early-stage, low-risk colorectal and breast cancer survivors (primary outcome), PROs (secondary outcome), and use of unplanned and non-recommended care (secondary outcomes). This trial will be conducted in a community-based integrated system, KPSC, with medical centers non-randomly assigned to the ePCP or usual care model, with the models running for up to 36 months. We will retrospectively (pre-period) and prospectively (post-period) identify early-stage breast and colorectal cancer patients at

all sites during their initial cancer treatment using a combination of pathology data and text information extraction algorithms. Potentially eligible survivors will be assigned a binary risk score (low risk/non-low risk) based on data readily available in the EMR including cancer stage, risk of recurrence, and other factors derived from current consensus-based recommendations. Embedded PCP participants will be transitioned to a trained PCP at 6-36 months after the cessation of active treatment. Multi-level components for this model include empirically-derived survivorship care interventions, such as provider education and training, using established training curriculum for PCPs engaging in survivorship care, health IT support (e.g., proactive office encounter alerts, links to guidelines), and patient education on the transition in care, signs and symptoms to be aware of, and what to expect from their PCP for surveillance and prevention. Usual care participants will be followed by their treating oncologist or surgeon, which is current "usual care" within KPSC.

Our specific aims and hypotheses (H) are:

Aim 1. To determine the efficacy of the PCP model relative to the usual care control group on receipt of recommended care (primary outcome). We will construct a composite measure of guideline-recommended cancer surveillance and age-appropriate preventive care services for the 18-month pre-period and 18-month post-period, identifying utilization from EMR data.

> H1. Patients in the PCP model will have superior receipt of recommended care compared to usual care.

Aim 2. To compare patient-centered outcomes on coordination of survivorship care, self-efficacy in managing care, and confidence in their PCP to provide survivorship care between the 2 models (secondary outcomes).

> H2. Patients in the PCP model will perceive significantly better care coordination, self-efficacy, and confidence in their PCP compared to usual care

Aim 3. To assess utilization of unplanned hospitalizations, use of urgent care, and receipt of non-recommended cancer surveillance services between the 2 models (secondary outcomes).

> H3. Use of unplanned and non-recommended care will be significantly less in the PCP model compared to usual care.

Exploratory Aim. We will explore PCP knowledge of and confidence in providing survivorship care, comparing PCPs who participate in the embedded PCP model to PCPs practicing at centers assigned to the usual care model.

Assignment and consent. Selection of participating centers will occur prior to PCP educational interventions and enrollment of patients. A scientifically valid comparison of the embedded PCP model to current usual care would only be possible with population-based enrollment and outcome assessment of low-risk survivors. Consequently, a waiver of the usual requirement for informed consent will be required. We believe that such a waiver of consent is not only widely recognized as necessary and appropriate 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). 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.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Despite widespread recognition and interest in survivorship in the U.S., there has been little research on models of survivorship care, or uptake of PCP survivorship models. Extant research has focused mainly on observational studies, such as the recent Patient-Centered Outcomes Research Institute (PCORI)-funded study "Evaluating different types of survivorship care" (study HSRP20143084, Mead et al.) that focused primarily on identifying model types among 236 Commission on Cancer-accredited organizations; a patient survey evaluated PROs. Findings indicate 3 major models of care (specialist consultative, mid-level provider longitudinal, and oncology-based) and few differences in PROs.[85, 86] While valuable, the study was not prospective, did not randomize, and did not evaluate important outcomes such as utilization. Eight 'Survivorship Centers of Excellence' were developed across the U.S. from 2006-11 with investment from the Lance Armstrong Foundation (one led by Dr. Patricia Ganz in collaboration with Dr. Hahn, Co-I and PI respectively for this proposal). These Centers implemented a variety of different models of care within their cancer centers, but did not conduct head-to-head comparisons of the models as a part of their implementation and research agenda.[87, 88] Multiple review papers and an AHRQ technical brief have categorized observed survivorship models of care and developed recommendations on potential model types, content, and structure.[2, 6, 10, 14, 15, 78, 79, 89-91] A review by Howell et al. determined that further research is needed to evaluate the efficacy of models of care;[15] McCabe et al. had a similar conclusion.[90] This paucity of high-quality research, particularly in community-based settings, seriously limits our ability to implement policy or practice decisions regarding survivorship care delivery, or to address the impact of clinician shortages and rising health care costs impacting systems, patients, and families.

4.3 JUSTIFICATION FOR INTERVENTION

Our proposed research builds on the foundational evidence from observational studies summarized above. Survivorship care provided by oncology specialists alone focuses on cancer surveillance and screening, but often lacks attention to preventive care or management of comorbid conditions. In contrast, care provided by PCPs is more likely to include age appropriate preventive care, as well as management of comorbid conditions and psychosocial concerns, without sacrificing timely detection of cancer recurrence or other adverse events, and may provide increased capacity and access to oncology services for newly-diagnosed patients.[25, 43-46] In our pilot study we found an embedded PCP model to be highly feasible and acceptable for low-risk patients.[57] Reviews of survivorship models have identified examples of primary care physician-led or "embedded PCP" models in the U.S., albeit a limited number.[79] These examples describe setting, domains of care, and care processes (e.g., strategy for managing long-term and late effects).[92, 93] However, as noted above, there are few, if any, evaluations of these models.

Collectively, this evidence demonstrates the feasibility and capability of PCPs assuming the primary role in providing survivorship care for early-stage, low-risk survivors, as well as the need for evaluation of survivorship care models. Thus, we will conduct a non-randomized pre/post with control trial to compare the effectiveness of an embedded PCP model, with a survivorship-trained PCP embedded into the oncology clinic to provide comprehensive survivorship care (e.g., cancer surveillance, symptom management, preventive care) as compared to an oncology-led model (usual care), where the survivor stays with their treating oncology team and sees their regular PCP in parallel, but in an uncoordinated fashion. We will address the barriers to PCP involvement identified in the empirical literature in the development of the intervention. Guided by the Framework for Quality Survivorship Care,[11] we propose to measure highly relevant outcomes including receipt of recommended care, PROs, including patient-provider communication and quality of life, and utilization of hospital, urgent, and non-recommended care.

4.4 END-OF-STUDY DEFINITION

A participant is considered to have completed the study if he or she has:

- Been identified and enrolled into either the ePCP or the oncology model of care
- Completed the 36-month follow-up period after enrollment into the intervention
- Completed the survey at 12-months post-transition (rolling recruitment)
- Truncated person-time will be accounted for in case of membership end or death

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

Provider population:
PCPs selected to participate must be Board Certified in a relevant specialty; hold a valid and current MD or advanced practitioner license; and be employed by the Southern California Permanente Medical Group (SCPMG).

Patient population:
- Adult (21+) KPSC members diagnosed and treated for pathologically-confirmed first primary early-stage breast (stage 0, I, II) or colorectal (stage I, II) cancer within KPSC
- Completed active cancer treatment within the past 6-36 months; active treatment includes cancer-directed surgery, chemotherapy (includes Herceptin (trastuzumab)), radiation therapy, and ovarian suppression therapy (e.g., Goserelin (Zoladex))
- Completed at least one office visit within KPSC medical oncology

- At low-risk for cancer recurrence and treatment-related toxicities based on stage of disease and treatment modalities

For our Aim 2 survey:

- Primary language of English or Spanish (although we will assess our Aim 1 participants for recorded preferred spoken language and adjust translations as needed)
- Ability to complete surveys of patient-reported outcomes

Individuals of all races, ethnicities, and genders are eligible for this study. Children will not be included in the study, because they are rarely, if ever, affected by breast or colorectal cancer.

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

- Pre-existing cancer diagnosis (other than non-melanoma skin cancer)
- Less than 120 days of KPSC membership after index diagnosis of primary breast cancer or colorectal cancer
- Patient undergoing workup for suspected primary cancer recurrence or new primary cancer
- Enrollment on other cancer clinical trial
- Received treatment indicative of metastatic or high-risk disease including breast cancer patients treated with neoadjuvent chemotherapy
- Serious medical or psychiatric condition that would detract from study participation and measurement of PROs

For the provider survey, there are no exclusions; all sex/gender, racial, and ethnic group members are eligible to participate.

5.3 LIFESTYLE CONSIDERATIONS

N/A

5.4 SCREEN FAILURES

We will retrospectively (pre-period) and prospectively (post-period) identify early-stage (stage 0-II) breast and early-stage (stage I, II) colorectal patients at our assigned intervention condition medical centers early in their treatment course using our comprehensive pathology database, Co-Path, combined with a text-information extraction system. We will identify the end of active treatment (surgery, chemotherapy, radiation, ovarian suppression injection treatment) using our treatment databases (e.g., Beacon chemotherapy, Mosaiq radiation) and EMR data. At the end of treatment, we will assess salient risk factors based on recent recommendations for stratifying low-risk survivors. We will create a risk-score (low

risk/non-low-risk) based on: stage of disease, risk of recurrence, treatment-related toxicity, and potentially pre-existing comorbidity burden, with assessment of potential interaction of treatment and comorbidity (e.g., breast patients with CVD who receive anthracyclines might be at high-risk for treatment-related CVD events). For patients enrolled in the intervention (post-period), we will send treating oncologists monthly lists of survivors to confirm as low-risk and eligible for the study; treating oncologists may have information beyond what is available in our structured EMR data that may affect risk status. Eligible survivors receiving care in embedded PCP model will receive an automated referral and patient education. This same identification algorithm will be applied to control centers to passively identify eligible patients and track utilization over time.

Screen failures are defined as participants with early-stage breast or colorectal cancer who are categorized as low-risk for recurrence and treatment toxicities but are subsequently determined to be not at low risk by either the treating oncologist or ePCP. Patients determined to be not at low-risk will be excluded from the study and will receive their survivorship care under usual care conditions, with their treating oncologist.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

For Aim 1, there is no individual participant recruitment or contact and patients will not be individually enrolled in this study; rather entire medical centers will be intervention or control with patients passively enrolled. We will prospectively identify early-stage (stage 0-II) breast and colorectal patients at our medical centers assigned to the intervention condition early in their treatment course to introduce the program and initiate tracking. Therefore, anyone who meets the eligibility criteria will be included in either the ePCP or usual care model. Our target enrollment size is 2450 subjects.

There are no specific strategies that will be used to recruit and retain historically under-represented populations in order to target sample size and conform with the *NIH Policy on Inclusion of Women and Minorities and Inclusion of Individuals Across the Lifespan as Participants in Research Involving Human Subjects.* Individuals of all races, ethnicities, and genders are eligible for this study. KPSC has an extremely diverse member population and no survivor would be excluded from participation in the care models based on spoken language (comprehensive interpreter services are available at all centers). KPSC patients are socioeconomically diverse with insurance coverage that includes commercial plans, Medicare Advantage, Medicaid, and individual insurance with options for high-, medium-, and low-deductible plans, and reside in urban, suburban, and rural communities. KPSC medical center characteristics are similar on distribution of age and gender, with distribution of race/ethnicity echoing the race/ethnicity distribution of Southern California.

Children will not be included in the study, because they are rarely, if ever, affected by breast or colorectal cancer.

Estimated distribution of age for early-stage breast and colorectal cancer survivors:

	Breast	Colorectal
Mean Age	61.2	65.3
<=40	5%	2%
41-50	16%	11%
51-60	26%	23%
61-70	31%	28%
71-80	17%	23%
81+	6%	13%

Identification of participants will begin in the 2nd quarter of Year 2.

Under Aim 2, we will use Dillman's Tailored Design Method to guide all survey activities including recruitment. This approach has three fundamental goals: 1) minimize all possible sources of survey error, including coverage, sampling, nonresponse, and measurement error. Our mixed mode approach will keep our sources of error low by reducing survey burden and increasing coverage; 2) tailor to the survey population by developing survey and recruitment methods that consider participant characteristics and that interact and work together to encourage response; 3) use procedures that create positive social exchange and encourage response. We designed our 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, text reminders), and incentives. Mixed-mode strategies such as the one we propose have been shown to be effective and efficient and help minimize total survey error. Key Tailored Design features of our approach include: sending a pre-incentive and promising completion incentives, using unified design elements across modes, using multiple modes of communication and multiple contacts, and using recruitment materials tailored for the study population (e.g., stressing the knowledge gained to improve cancer survivorship care).

Participants will receive a $20 gift card for completing the survey. These are nominal incentive levels widely used in current studies within our department for survey completion; therefore, we anticipate no undue influence or coercion by providing this level of incentive to potential participants.

The invitation letter will include a short URL for the web survey leading directly to the survey and will include a toll-free number and email for opting out of further contact or asking questions. We will use KPSC branding to provide legitimacy for KPSC members. The letter will stress the potential impact of knowledge gained from the survey in helping future cancer survivors and the importance of the participant's expertise in this topic, following social exchange theory principles. We will also indicate our intention to share the results with participants to further establish trust and improve response. We will include a self-addressed stamped return envelope for paper surveys. Non-responders will be sequentially contacted first by email and/or text message (when available), mail (with a paper survey included), and finally by telephone (for an interviewer-administered survey).

A secure internal study database will permit us to track the recruitment status of each member of the original survey sample at every phase. We will conduct rolling recruitment over a 1-year period by making ordered contacts in waves. Using real-time reporting, we will continually assess response rates and adjust the timing and order of contacts, as needed, to most effectively achieve the desired sample size and diversity (i.e. sex, race/ethnicity). The content of recruitment materials may also be modified based on participants' feedback and response. By employing multiple avenues for recruitment (mail, phone, and email), we can ensure a strong response.

For Aim 3, there is no participant contact; we will obtain utilization data from the KPSC electronic medical record and associated research databases for eligible participants at the embedded PCP (experimental) and usual care arm. This aim is to determine utilization of unplanned hospitalizations, urgent care, and non-recommended cancer surveillance services, using CPT and ICD codes to identify hospitalizations related to cancer, use of urgent care, and use of non-recommended care. Non-recommended care measures will be identified from relevant guidelines (e.g., ASCO Choosing Wisely, American Cancer Society (ACS) Survivorship guidelines).

Exploratory Aim. We will invite our ePCPs and a random sample of PCPs from our both arms arm to participate in a brief, online survey of knowledge and confidence in cancer survivorship care. Recruitment methods for KPSC clinicians will include email, letter, and/or telephone outreach. The overall PCP population at KPSC (N=2,932) consists of 34% white, 49% Asian, 11% Hispanic, and 5% black; 48% are female. We anticipate our PCP sample at participating centers to reflect these characteristics.

Retention.
Aims 1 and 3 will rely on a passive retention approach, as there is not participant contact and patients will not be individually enrolled in this study. Patients who maintain active KPSC membership status will be retained.

Under Aim 2, retention is not applicable, because the PRO survey is a one-time cross-sectional study; we will invite all eligible survivors to participate in the PRO survey at 12 months after their transition to the ePCP or the oncology model. Therefore, we do not propose active follow-up of participants who participate in this one-time survey.

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

Embedded PCPs will provide comprehensive care for survivors, including cancer surveillance services, preventive care, and management of long-term therapy and associated side effects (e.g., ongoing

endocrine therapy in breast survivors). We have designed a comprehensive multilevel approach to prepare survivors and PCPs (physicians and/or advance practice providers).

Intervention: Embedded PCP. We will enroll ePCPs in a 4-month course of initial training and education, followed by ongoing education via tailored survivorship information for low-risk survivors transitioning to their care. We will use widely and freely available resources to help ensure generalizability and scalability of the training approach. Initial training features 3 core components to build capacity, skill, and knowledge, guided by the ASCO Core Curriculum for Survivorship Training: 1) Individual didactic learning; 2) Small in-person group sessions; and 3) Observation. For individual learning, we will use the "Cancer Survivorship E-Learning Series for Primary Care Providers" training modules, a freely available online educational series developed by expert clinicians, researchers, and survivors at the National Cancer Survivorship Resource Center in collaboration with the ACS. Next, small group sessions with the research team, including clinical co-investigators from primary care and oncology, to review survivorship resources and address questions for 60 minutes each session for 4 weeks, with pre-session work of 1-2 hours per week for sessions 1-3. Lastly, observational learning will take place via shadowing oncologists for 5-10 hours per week for 2 weeks, again leveraging PCP education time, and attending tumor boards (ongoing). We will conduct a brief annual online survey to assess PCP knowledge and confidence in survivorship care and will compare ePCPs to PCPs in the usual care arm (Exploratory Aim). When survivors transition to the ePCP, we will include a tailored packet of educational information and reminders for the ePCP: the ACS survivorship guidelines for breast or CRC cancer, which are designed to assist PCPs in care of survivors. We will include a standardized letter reminding the ePCP about goals of care and how to work with the oncology team. Importantly, this letter will include when to refer the survivor back to oncology/surgery. Typically, this will include unremitting symptoms such as shortness of breath or pain.

Intervention: Patient-level. Eligible patients in the ePCP model will be provided with tailored education regarding the planned transition prior to the transition, a critical factor according to our formative evaluation. After cessation of active treatment, the care team will provide printed information including the planned course of survivorship care, what to expect from ePCP care, when the transition will occur, and reassurance that the oncology team will be available via telephone and email, and that PCPs will refer back to the oncologist for any concerning signs or symptoms. This will be mailed to participants and/or provided by their treating oncologist, included as part of the standard KPSC survivorship binder provided at the end of treatment, as well as uploaded to the kp.org patient portal.

Intervention: System-level. Working with our health IT team, we will create tailored alerts in the EMR for recommended cancer surveillance and preventive care services that include rationale, links to guidelines, and references for questions. These will fire when survivors have an outpatient office visit with their ePCP.

6.1.2 ADMINISTRATION AND/OR DOSING

Intervention: Embedded PCP. We will engage ePCPs in a 4-month course of initial training and education, followed by ongoing education via tailored survivorship information for low-risk survivors transitioning to

their care. Initial training features 3 core components to build capacity, skill, and knowledge: 1) Individual didactic learning; 2) Small in-person group sessions; and 3) Observation.

Embedded PCP survivorship training activities		
Weeks 1-8	Didactic learning from online survivorship care for PCPs modules[94]	
Module 1, 2	Overview; role of PCPs	Late effects, symptom management
Module 3, 4	Psychosocial needs	Preventive care
Module 5, 6	Care coordination	Cancer recovery
Module 7, 8	Colorectal survivors	Breast survivors
Weeks 9-12	Small group sessions with research team and clinical leaders	
Session 1	Health and wellness for cancer survivors: Live webinar lead by KPSC physicians with Q&A	
Session 2	Signs and symptoms of local disease recurrence, managing pain: Live webinar lead by KPSC physicians with Q&A	
Session 3	Working up potential breast cancer recurrence; unusual presentations of metastatic disease: Live webinar lead by KPSC physicians with Q&A	
Session 4	Managing long-term endocrine therapy: Live webinar lead by KPSC physicians with Q&A	
Session 5	Risk reduction and cancer prevention for survivors: Live webinar lead by KPSC physicians with Q&A	
Session 6	Review available resources and discuss current educational/resource needs, health IT support, other ad hoc questions Includes: *ACS Survivorship Guidelines, Long-Term Survivorship Care After Cancer Treatment[95]; From Cancer Patient to Cancer Survivor: Lost in Transition[96]; Cancer Survivorship in Primary Care* [97]; *ASCO Treatment Plan and Summary Resources*[12, 98]	
Session 7	Colorectal cancer survivorship and recurrence: Live webinar led by KPSC physicians with Q&A	
Weeks 13-16	Observation	
Weeks 13-14	Shadow breast and colorectal oncologists to observe cancer care processes	
Weeks 13-16+	Attend tumor boards and oncology staff meetings	
Care transition	Provided with survivorship resource guide	
Evaluation	Brief online survey on perceived confidence and knowledge of survivorship care;[60] evaluation of training content	

When survivors transition to ePCP care, our ePCPs will have a tailored resource packet to guide care, including links to relevant guidelines for breast or CRC cancer, which are designed to assist physicians in care of survivors (e.g., the National Comprehensive Cancer Network surveillance guidelines), oncology team information (e.g., department chief, oncology social workers), and local available resources.

Intervention: Patients. After cessation of active treatment, the care team will provide information about the ePCP survivorship clinic along with a letter from the treating oncologist describing what to expect from ePCP care, when the transition will occur, and reassurance that the oncology team will be available via telephone and email, and that PCPs will refer back to the oncologist for any concerning signs or symptoms. This will be mailed to participants and/or provided by their treating oncologist, included as

part of the standard KPSC survivorship binder provided at the end of treatment where possible/applicable, as well as uploaded to the patient's kp.org portal.

Intervention: System-level. Health IT alerts will fire when survivors have an outpatient office visit with their embedded PCP using the same programming methodology as for oncology visits.

6.2 FIDELITY

6.2.1 INTERVENTIONIST TRAINING AND TRACKING

We will assess center compliance with the study protocol monthly, with review of relevant data. We will collect utilization data for services with the ePCP, the treating oncology team, and with the patient's assigned KPSC PCP. We will check for patterns of utilization indicative non-compliance with the ePCP protocol (e.g., no or limited visits with the ePCP, continued use of oncology for patients in the ePCP arm). We will have regular interactions with the study sites to discuss and review these data.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

N/A. This is quasi-experimental pre/post with control group design.

6.4 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION ADHERENCE

Participant adherence at the patient level does not apply to this study. Participants may or may not have visits with their ePCP and/or oncology team.

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 ePCP model 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 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 EPICS 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

For our utilization aims (Aim 1, 3) we will track all utilization within KPSC until disenrollment or death.

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

The following actions must be taken if a participant fails to return the survey:

- The site will attempt to contact the participant, 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 (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 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.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 ENDPOINT AND OTHER NON-SAFETY ASSESSMENTS

Background Characteristics and Potential Confounders. 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 EMR for all participants. Self-reported demographics will be collected from those who participate in the PRO survey. We will collect for clinician variables such as clinician gender, race, and years in practice from the EMR. Sex as a potentially important biologic factor will be included in all analyses.

Receipt of Recommended Care (Aim 1). We will construct composite measures of recommended care for cancer surveillance and for preventive care, based on recommendations from the NCCN survivorship guideline. Cancer surveillance for early-stage breast cancer includes annual mammography and 2-4 physician visits with history and physical (H&P) for the first 3 years; CRC surveillance includes colonoscopy within first year, annual chest/abdominal/pelvic CT, and 2-4 H&P visits and CEA lab tests annually for the first 3 years. Preventive care measures will be based on United States Preventive Task Force recommendations including appropriate cancer screening (other than for surveillance of primary cancer) for CRC, cervical, breast, and lung cancers, vaccinations (flu, pneumococcal), counseling for smoking cessation, and management of hyperlipidemia and hypercholesterolemia. These recommendations will be tailored to individual age, cancer type, health behaviors, and prior care (e.g., for breast cancer survivors ≥50, colonoscopy every 10 years or annual FIT Kit for CRC cancer screening). We will use validated algorithms from our prior work based on CPT and ICD codes to identify use of services.[17, 31, 32, 99-102] We will identify receipt of recommended care for up to 36 months, starting 12 months after cessation of active treatment. Recommended care will be assessed in 12-month periods, with a binary outcome of received/did not receive for recommended cancer surveillance and for preventive care. We will also compare rates of individual services (e.g., rates of vaccination). Survivors with a pattern indicative of recurrence, based on validated recurrence algorithms,[103, 104] will be excluded from analysis of recommended cancer care. We will identify use of services from oncology, ePCP, and the member's assigned KPSC PCP to evaluate the impact of the model on utilization of services.

Patient Reported Outcomes (Aim 2). We will use validated, reliable measures from existing national surveys that have been used in our target population. Most measures come from well-established surveys such as the Medical Expenditure Panel Survey (MEPS), the European Organisation for the Research and Treatment of Cancer (EORTC) Quality of Life, the Consumer Assessment of Healthcare Providers and Systems (CAHPS), and the Patient-Reported Outcomes Measurement Information System (PROMIS). We will assess patient-reported coordination of care, patient-provider communication, physical and mental health, assessment of survivorship care delivery, satisfaction with health decisions, and other measures relevant to survivorship care. We will also collect socioeconomic, demographic, and health behavior data (e.g. smoking). To evaluate our secondary outcome of patient-provider communication and coordination, we will use validated measures from the MEPS Experiences with Cancer Supplement CAHPS surveys (i.e., Patient-Centered Medical Home CAHPS coordination items). 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, with response options discussed in detail, briefly discussed, did not discuss, and I don't remember. We will also examine CAHPS care coordination that includes six items on how often providers had appropriate information about: care provided by specialists; medical records and information about care; patient prescriptions and medications; follow-up regarding patient labs, X-rays, or other tests; and managing care between different providers. The response set for these items is a 4-point Likert scale ranging from "Never" to "Sometimes" to "Usually" to "Always." We will use design principles of Dillman et al. to order questions to minimize testing order effects, ensure the survey is appropriately and consistently designed for multiple modes, and minimize participant burden.[105]

Measures for Key Constructs for Patient Survey All measures have been previously validated and used in cancer research	
Construct	**Measure**
Patient-provider communication about survivorship care	Medical Expenditure Panel Survey (MEPS) 2016, Experiences with Cancer Supplement, Section 7, Medical Care for Cancer[106]
Quality of life	European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC)[107]
Coordination and continuity of cancer care	Cancer Consumer Assessment of Healthcare Providers and Systems (CAHPS)[108]
Self-efficacy	PROMIS self-efficacy for managing symptoms[109]
Overall health	PROMIS Global Health Scale[109]
Receipt of treatment summary and/or care plan	Receipt of treatment summary from Health Information and National Trends Survey (HINTS 4, Cycle 2)[110, 111]
Delivery of survivorship care	Delivery of Survivorship Care Scale[63]
Symptom burden	Patient-Reported Bother From Side Effects of Cancer Therapy[112]
Satisfaction with health care decisions	Patient satisfaction with health care decisions: the satisfaction with decision scale[113]
Confidence in care	Questions adapted from 'Confidence in managing survivorship care' Casillas et al[114]

Utilization of unplanned hospitalizations, urgent care, and non-recommended cancer surveillance services (Aim 3). Using a similar approach to Aim 1, we will use CPT and ICD codes to identify hospitalizations related to cancer, using primary ICD code to identify reason for admission, as well as use of urgent care and use of non-recommended care. Non-recommended care measures are identified from relevant guidelines (e.g., ASCO Choosing Wisely, ACS Survivorship).[115-117] For early-stage breast cancer, this includes serum tumor markers and high-intensity imaging (e.g., CT and PET scans); for CRC, PET scans.

Exploratory Aim. We will explore PCP knowledge of and confidence in providing survivorship care, comparing the embedded PCPs to PCPs practicing at centers assigned to the usual care model.

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)/Data 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

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.

Because patients with early stage cancer will be enrolled in the study, we expect that approximately 2-5% of breast cancer survivors will have a breast cancer recurrence [118], and 5-15% of colon and rectal cancer survivors will have a recurrence. [119] We expect this rate to be comparable across study arms. In terms of cancer-related mortality, the 5-year relative survival for localized breast cancer is 99% and regional is 86%; for colon and rectal cancers the localized 5-year relative survival is 91% and regional is 72%. [120] Our study will follow patients for up to 36 months, thus we anticipate cancer-related mortality in each arm; again, we expect these to be comparable in both arms. Cancer-related hospitalization outside of hospitalization related to cancer recurrence will be very rare, as these patients will be 12 months out from their active treatment (surgery, chemotherapy, radiation, ovarian suppression injection). We will capture metrics on cancer recurrence, mortality, and hospitalizations as part of our safety monitoring plan.

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.

Expected Risks. Based on data from randomized controlled trials and observational studies, [81, 82, 84, 121-123] we expect the SAEs rate to be comparable across study arms. These clinical events are risks inherent in the population and would occur regardless of study enrollment. We do not expect that the risk of adverse outcomes is heightened as a function of being enrolled in the study. Risks associated with collection of PRO data and potential loss of confidentiality and study procedures to minimize such risks were reviewed above.

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 Principal Investigator 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 Principal Investigator 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 Principal Investigator'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 presenting for medical care within the embedded PCP or the oncology model.

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 Principal Investigator 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 Principal Investigator 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 Principal Investigator 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 Principal Investigator 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 Principal Investigator 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 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 Principal Investigator 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

Primary Endpoint(s):
To determine the efficacy of the ePCP model relative to the usual care group on receipt of recommended care. We will construct a composite measure of guideline-recommended cancer surveillance and age-appropriate preventive care services, identifying utilization from EMR data. We hypothesize that patients in the ePCP model will have superior receipt of recommended care compared to usual care.

Secondary Endpoint(s):

1) To compare patient-reported outcomes (PROs) including patient-provider communication, coordination of survivorship care, and quality of life between the two models. We hypothesize that patients in the ePCP model will perceive significantly better care communication, self-efficacy, and confidence in delivery of survivorship care compared to usual care, as collected by PRO surveys.

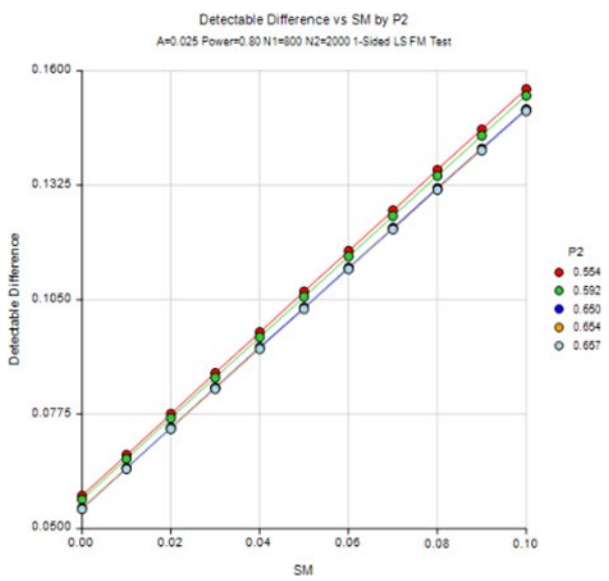
2) To compare utilization of unplanned hospitalizations, use of urgent care, and receipt of non-recommended cancer surveillance services between the two models. We hypothesize that use of unplanned and non-recommended care will be significantly less in the ePCP model compared to usual care.

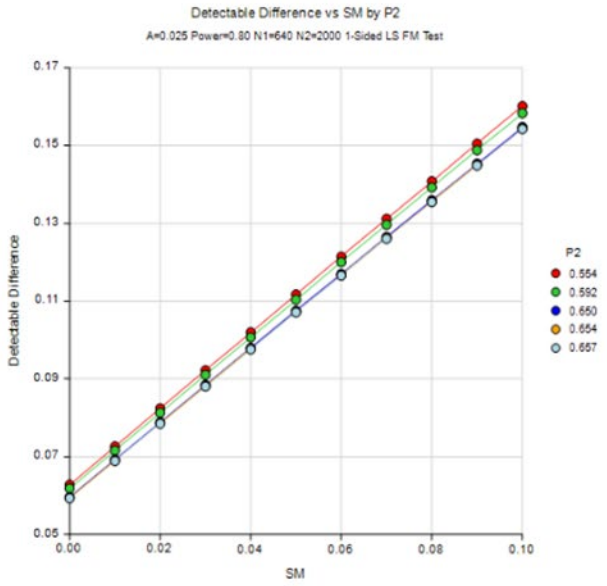
9.2 SAMPLE SIZE DETERMINATION

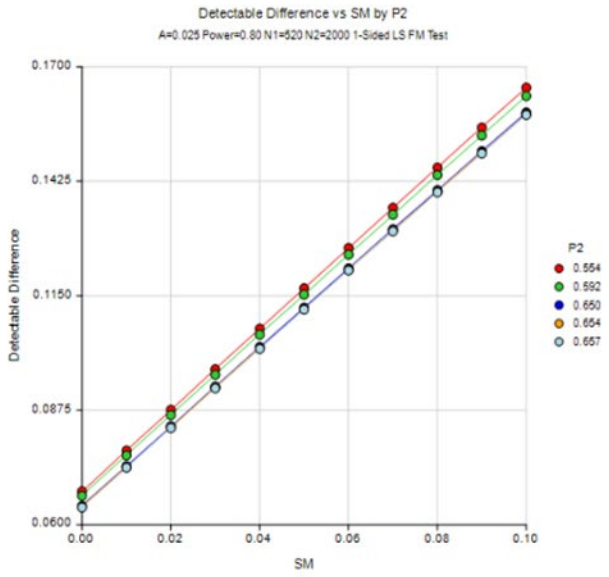
Based on recent literature, expected prevalence of surveillance items in the first year of breast cancer survivorship range from 15% for assessment of bone health to 80% for mammography.[124] For CRC surveillance, a meta-analysis has shown that adherence ranged from 18-61% for colonoscopy and 17-71% for CEA tests. For preventive measures, Snyder et al. found that 30% of breast cancer survivors received recommended CRC screening, 32% received lipid testing, and 53% received an influenza vaccine. In our original cluster randomized design, we had 8 total medical centers, 4 intervention and 4 control, and anticipated 2,000 patients (approximately 250 per site). Under the original design, we modeled a range of expected values from 15% to 80% and found that a study this size would provide 90% power to reject the null hypothesis when the mean difference between groups is between 5.5% and 7.2%, with computed minimum detectable effect sizes for fixed power (0.8) and level of significance (0.025), using superiority hypotheses for the primary (receipt of recommended care) and secondary (patient-reported) outcomes.

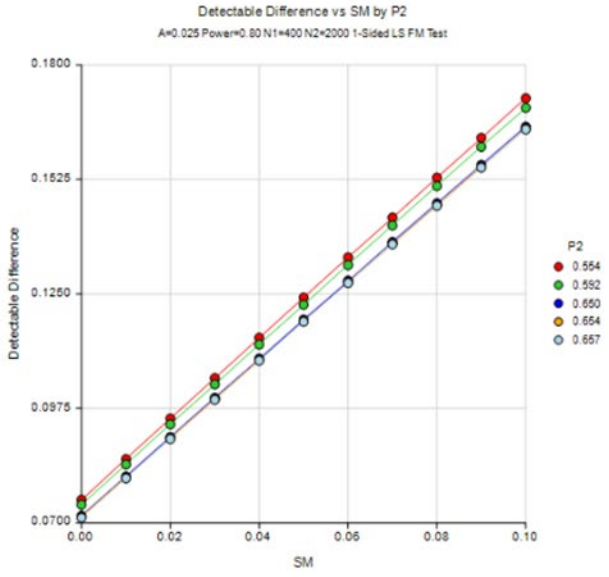
As we expect the embedded PCP model to provide more comprehensive care, superiority hypotheses for these outcomes are warranted.

Receipt of recommended care (Aim 1):. Our new study design, necessitated by pressures from the COVID pandemic, is a quasi-experimental pre/post with control group design. While we have lost the element of randomization, we have increased our number of participating medical centers from 8 to 14 and increased our anticipated number of participants to 2450. We have also added a pre-period analysis of health care utilization (Aims 1 and 3) for early-stage breast and colorectal cancer patients in survivorship between 2015-2019. We will use difference-in-difference (DID) analyses to compare the average changes pre- vs post-implementation and between the study arms. Assuming, rather conservatively, that there will be no pre-period differences in receipt of recommended care across the 14 study sites (4 treatment, 10 control), we calculated the minimum detectable differences that could achieve 80% power to detect superiority (varying the superiority margin from 0% to 10%), assuming no clustering and a level of 0.025. Given the accrual challenges noted above, we used our new sample size expectations to re-calculate the minimum detectable differences, which previously ranged from about 5.5% to 15.6% across the range of superiority margins. Based on our current projected accrual, these differences now fall in the range of being as small as 6% to 16% for our most optimistic projection (640 intervention patients), and as large as 7.6% to 16.5% for our least optimistic projection (450 intervention patients). Should we observe significant pre-period differences between arms, the minimum detectable differences reported here will be over- or under-estimated depending on the direction and magnitude of the former.





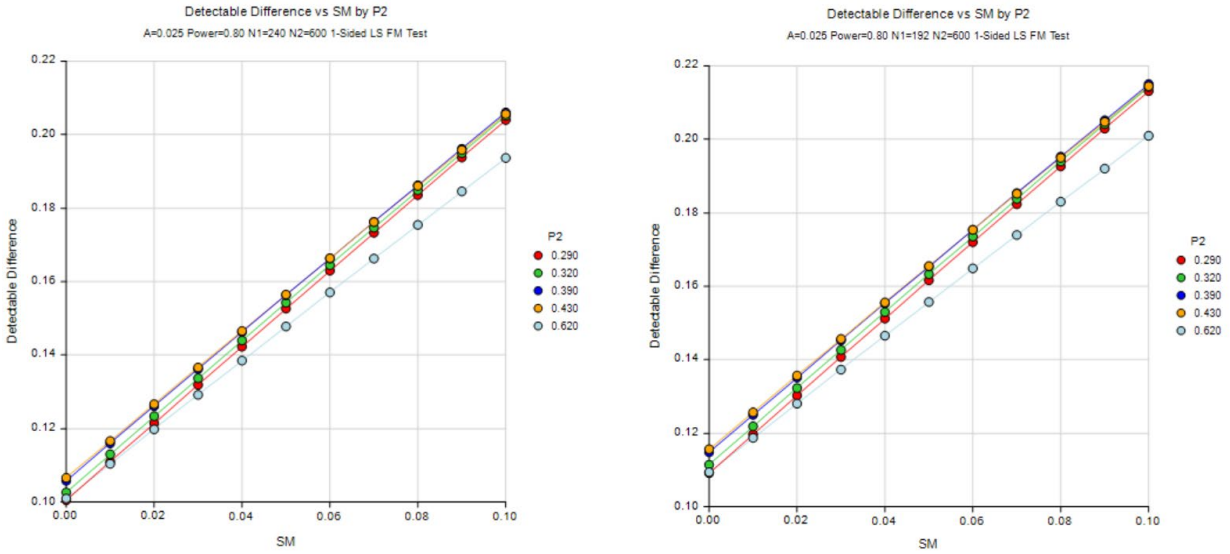




Legend
PD = baseline score for 5 different sub-scores on proportion scale
SM = superiority margin

PROs (Aim 2):

Based on our prior experience with this population, we anticipate a 30% survey response rate with an estimated 840 responders. For our secondary outcome of patient-provider communication, from prior studies using the MEPS measure we expect that 32% of patients will report high-quality communication, with responses to individual questions ranging from 29% to 62%. As for Aim 1 above, we re-estimated the minimum detectable differences to reflect our current projected accrual, and under the same response rate assumptions, our sample size expectation for the intervention group is now 192. In order to achieve 80% power to detect superiority (varying the superiority margin from 0% to 10%), the smallest detectable difference for patient-provider communication ranges from 10.9% to 21.5%, under the alternative hypothesis that the primary care group is superior to usual care. The minimum detectable differences for the individual questions fall within a similar range. These further assume no clustering and a significance level of 0.025.



Legend
PD = baseline score for 5 different sub-scores on proportion scale
SM = superiority margin

For Aim 3, we will use CPT and ICD codes to identify hospitalizations related to cancer, using primary ICD code to identify reason for admission, as well as use of urgent care and use of non-recommended care. Non-recommended care measures are identified from relevant guidelines (e.g., ASCO Choosing Wisely, ACS Survivorship).[115-117] For early-stage breast cancer, this includes serum tumor markers and high-intensity imaging (e.g., CT and PET scans); for CRC, PET scans.

9.3 POPULATIONS FOR ANALYSES

The analyses will follow an intent-to-treat (ITT) strategy, i.e. analyses will include all survivors in the groups to which their medical centers were assigned, regardless of their individual adherence with the model.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

Descriptive statistics will be calculated prior to conducting the primary analyses, and these will be compared between the pre- and post-implementation periods to assess for potential imbalances in patient and caregiver characteristics. For all analyses, data consistency and assumptions required, e.g., normality of responses, will be checked. Any data transformation or alternative methods necessary to analyze the data will be determined by examining the data structure. Individual patients and caregivers will be the unit of analysis. To address the fact that our study design will now be pre-post with a control group, the primary analytic approach will be difference-in-differences (DID), as it will be of specific interest to compare the average changes pre- vs post-implementation between the study arms. The analytical plans corresponding to the major study aims are detailed below. We expect minimal missing data for baseline patient and provider characteristics and will respectively use mean/median or reference group imputation for continuous and categorical covariates. While this approach has potential for introducing bias, some of those biases may be "differenced out" in the DID models, especially those for which we have measurements on the same patients or providers in both time periods. As a sensitivity analysis, we will compare the results from that approach to complete case analysis for primary outcomes. We also expect that baseline differences in potential confounders will also be "differenced out", at least at the medical center level and likely at the provider level too, save for some providers who either may not be in our system during both study periods, or who may cross study arms over time. Given that confounding and selection bias (mainly for PROs) due to patient characteristics may be unavoidable, we will explore the use of propensity-score based approaches (IPTW, matching weights, etc.) for addressing these concerns.

9.4.2 ANALYSIS OF THE PRIMARY ENDPOINT(S)

For utilization data in both the pre- and post-periods, we will construct a composite measure of recommended care for cancer surveillance and for preventive care, based on recommendations from the ACS survivorship guideline. Cancer surveillance for early-stage breast cancer includes annual mammography and 2-4 physician visits with history and physical (H&P) for the first 3 years; CRC surveillance includes colonoscopy within first year, annual chest/abdominal/pelvic CT, and 2-4 H&P visits and CEA lab tests annually for the first 3 years. Preventive care measures will include appropriate cancer screening (other than for surveillance of primary cancer) for CRC, cervical, breast, and lung cancers, vaccinations (flu, pneumococcal), counseling for smoking cessation, and management of hyperlipidemia and hypercholesterolemia. These recommendations will be tailored to individual age, cancer type, health

behaviors, and prior care (e.g., for breast cancer survivors ≥50, colonoscopy every 10 years or annual FIT Kit for CRC cancer screening). We will use validated algorithms from our prior work based on CPT and ICD codes to identify use of services.[17, 31, 32, 99-102] We will identify receipt of recommended care for up to 36 months, starting approximately 12 months after cessation of active treatment (see Study Timeline, section 2.7 of the Study Record). Recommended care will be assessed in 12-month periods, with a binary outcome of received/did not receive for recommended cancer surveillance and for preventive care. We will also compare rates of individual services (e.g., rates of vaccination). Survivors with a pattern indicative of recurrence, based on validated recurrence algorithms,[103, 104] will be excluded from analysis of recommended cancer care. We will identify use of services from oncology, embedded PCP, and the member's assigned KPSC PCP to evaluate the impact of the model on utilization of services.

For the primary outcomes, we will use the DID framework (see equation 1) with different link functions to address the different types of outcomes (continuous, categorical, or counts). Outcome measurements are denoted yijkt, where i indexes the individual patients, j indexes the providers with whom patients had follow-up visit at site k, and during study time period t. The first two parameters on the right-hand side of equation 1 denote a random clinician intercept (δ0j) to represent the baseline variation between physicians in receiving recommended care, and δ1 denotes the level difference for the Oncology-led model of care at the beginning of the post-implementation follow-up period. The other two DID parameters δ2 and δ3 specify the average difference between Embedded-PCP and Oncology-led models at baseline and the difference-in-differences, the latter of which is the main quantity of interest. The remaining parameters correspond to a flexible function of time, and fixed effects for respective patient, provider, and site characteristics.

Equation 1: $f(\mathrm{E}(y_{ijkt})) = \delta_{0j} + \delta_1 I(post=1) + \delta_2 \boldsymbol{I}(Embedded\ PCP=1) + \delta_3 \boldsymbol{I}(post=1)\boldsymbol{I}(Embedded\ PCP=1) + f(t) + \boldsymbol{X_i\alpha + X_j\beta + X_k\gamma}$

Aim 1: n1=800, n2=2000

		Minimum δ by Superiority Margin										
Subscore	Mu_0	0	0.01	0.02	0.03	0.04	0.05	0.06	0.07	0.08	0.09	0.1
Breast, F	0.65	0.055	0.065	0.074	0.084	0.094	0.103	0.113	0.122	0.132	0.141	0.151
Colorectal, F	0.657	0.055	0.064	0.074	0.084	0.093	0.103	0.112	0.122	0.131	0.141	0.150
Colorectal, M	0.592	0.057	0.067	0.077	0.086	0.096	0.106	0.115	0.125	0.135	0.144	0.154
General, F	0.654	0.055	0.064	0.074	0.084	0.093	0.103	0.112	0.122	0.132	0.141	0.151
General, M	0.554	0.058	0.068	0.078	0.087	0.097	0.107	0.117	0.126	0.136	0.146	0.156

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

The main outcomes for Aim 2 will be analyzed using the same general modeling approach outlined in Equation 1, but dropping the parameters for the time difference and difference-in-difference(δ_1 and δ_3) since we will only be measuring those items once during follow-up. In this case, for example, yijk could denote the probability that patient i reports 'high quality' patient-provider communication during study period k. Other parameters in the model may be interpreted in the same manner as described above.

Aim 2: n1=240, n2=600

Subscore	Mu_0	0	0.01	0.02	0.03	0.04	0.05	0.06	0.07	0.08	0.09	0.1
Pat-Prov Communication	0.32	0.103	0.113	0.123	0.134	0.144	0.154	0.164	0.175	0.185	0.195	0.205
Surveillance	0.62	0.101	0.110	0.120	0.129	0.138	0.148	0.157	0.166	0.175	0.185	0.194
Late Effects	0.43	0.106	0.116	0.126	0.136	0.146	0.155	0.165	0.175	0.185	0.194	0.204
Emotional Concerns	0.29	0.102	0.113	0.123	0.133	0.143	0.154	0.164	0.174	0.184	0.194	0.204
Lifestyle Behaviors	0.39	0.106	0.116	0.126	0.136	0.146	0.156	0.166	0.176	0.185	0.195	0.205

Outcomes for Aim 3 will follow the same approach as Aim 1, but for categorical outcomes such as any inpatient visits, while using linear or log link functions where needed for continuous or count outcomes.

9.4.4 SAFETY ANALYSES

N/A

9.4.5 BASELINE DESCRIPTIVE STATISTICS

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 EMR for all participants and compared between intervention and control groups.

9.4.6 PLANNED INTERIM ANALYSES

N/A

9.4.7 SUB-GROUP ANALYSES

We will test for differences by gender and race/ethnicity between the intervention and control groups on utilization and patient-reported outcomes. Prior studies of utilization in cancer survivors do not suggest or negate significant differences in intervention effect among subgroups; thus, it is important for our study to examine potential differences.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

We will not tabulate individual participant data.

9.4.9 EXPLORATORY ANALYSES

We will explore PCP knowledge of and confidence in providing survivorship care, comparing the embedded PCPs to PCPs practicing at centers non-randomly assigned to the usual care model. We will compare embedded PCPs to usual care PCPs using 2-sided chi-square tests.

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 for informed consent will be required to ensure a scientifically valid comparison of the ePCP model to current usual care. We do not foresee any risks to potential participants by not directly consenting them to participate in the trial. This study poses minimal risk to the patient because survivorship cancer care will be performed as part of routine medical care, and both the ePCP and the oncology-based model for survivorship cancer care are consistent with guidelines from professional societies and organizations with regard to the delivery of safe, appropriate, and usual care practices. 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).

Patients will be recruited for PRO surveys under Aim 2. We will obtain written or oral consent from all participants for participation in the surveys. Survey consents and opt out options will be built into an electronic template as part of the initial survey screens. Consent forms describing in detail the survey procedures, and risks will be given to the participant and written or oral documentation of informed consent will be completed prior to completing the survey. The following consent materials are submitted with this protocol [none at this time; however, all written or oral consenting procedures will be submitted to our IRB prior to conducting any patient contact for the surveys under this Aim.

For utilization data captured under Aim 3 from the EMR, individual patients will not be recruited or consented (falling under the waiver of informed consent for Aim 1).

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

For Aims 1 and 3, consenting procedures are not applicable.

For Aim 2, consent forms describing in detail the survey procedures, and risks will be given to the participant, and written or oral documentation of informed consent will be completed prior to completing the survey.

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 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 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://www.citiprogram.org/default.asp) 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 Principal Investigator 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. We will invite other investigators to submit ancillary study proposals using the data from the study.

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 datasets. 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.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

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We have assembled an Advisory Board with expertise in complementary areas to the study team. We will also include patient members who have experienced cancer, recruited through the KPSC Regional Member Advisory Committee. The role of the Board will be to provide input and guidance on the overall study design and progress, including refinement of model components (e.g., PCP training, health IT alerts), measurement of outcomes, and discussion of results. We will convene quarterly advisory board meetings each year. We will rely on stakeholder engagement strategies to ensure that our work is relevant and responsive, following the general approach of the Six Stage model for engagement.

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, 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 embedded PCP or oncology model (standard of care) arm under Aim 1.

We have appointed a Data and Safety Monitoring Board (DSMB) consisting of a biostatistician, a cancer epidemiologist, and an oncologist. The DSMB will meet with the investigators during the start-up phase to approve the final study protocol. Yearly meetings will occur via conference calls to monitor recruitment and adverse events.

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, not applicable. The medical center sites will not consent participants under Aim 1.

- Aim 2, consenting for the PRO survey will be managed by the research study team (study staff will review both the documentation of the consenting process as well as a percentage of the completed consent documents). This review will evaluate compliance with GCP, accuracy, and completeness. Feedback will be provided to the study team to ensure proper consenting procedures are followed.
- Aim 3, not applicable.

Source documents and the electronic data --- Data for this study are obtained from clinical and administrative databases (Aim 1) and participant self-report for the surveys (Aim 2). For utilization data under Aim 3, we will use a similar approach to Aim 1 – e.g., CPT and ICD codes will be used to identify hospitalizations related to cancer, use of urgent care, and use of non-recommended care. Non-recommended care measures will be identified from relevant guidelines (e.g., ASCO Choosing Wisely, ACS Survivorship). We will collect data in order to initiate participation identification at all sites in Years 1 and 2 (Aim 1); we will collect PRO survey data in Years 2-4 (Aim 2); we will collect utilization data in Year 5 (Aim 3).

Intervention Fidelity — We will assess compliance with the study protocol monthly, with review of relevant data. We will collect utilization data for services with the ePCP, the treating oncology team, and with the patient's assigned KPSC PCP. We will check for patterns of utilization indicative non-compliance with the ePCP protocol (e.g., no or limited visits with the ePCP, continued use of oncology for patients in the ePCP arm). We will have regular interactions with the study sites to discuss and review these data.

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 Principal Investigator 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 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 EMR for all participants (Aim 1) by study programmers under the oversight of Dr. Hahn. Self-reported demographics will be collected from those who participate in the PRO

survey (Aim 2). We will collect clinician variables such as clinician gender, race, and years in practice from the EMR.

Clinical EMR data on utilization (Aim 3) 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/default.asp) 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 Principal Investigator 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 Dr. Erin E. Hahn. Considerations for ensuring confidentiality of these shared data are described in **Section 10.1.3**.

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 teamproper 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 Principal Investigator 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 the National Cancer Institute (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
ACS	American Cancer Institute
AHRQ	Agency for Healthcare Research and Quality
ASCO	American Society for Clinical Oncology
CAHPS	Consumer Assessment of Healthcare Provider and Systems
CEA	Carcinoembryonic Antigen
CFR	Code of Federal Regulations
CITI	Collaborative Institutional Training Initiative
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CRC	Colorectal Cancer
CRF	Case Report Form
CVD	Cardiovascular Disease
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
EORTC	European Organisation for the Research and Treatment of Cancer
EMR	Electronic Medical Record(s)
ePCP	Embedded Primary Care Physician
FITKit	Fecal Immunochemical Test Kit
GCP	Good Clinical Practice
H&P	History and Physical
HIPAA	Health Insurance Portability and Accountability Act
ICC	Intracluster Correlation
ICD	International Classification of Diseases
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
IT	Information Technology
ITT	Intent to Treat
KPSC	Kaiser Permanente Southern California
MEPS	Medical Expenditure Panel Survey
MOP	Manual of Procedures

NCI	National Cancer Institute
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
PCORI	Patient-Centered Outcomes Research Institute
PET	Positron Emission Tomography
PHI	Protected Health Information
PO	Project Officer
PROs	Patient-Reported Outcomes
PROMIS	Patient-Reported Outcomes Measurement Information Systems
QA	Quality Assurance
QC	Quality Control
RCT	Randomized-Controlled Trial
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SCPs	Survivorship Care Plans
SCPMG	Southern California Permanente Medical Group
SMC	Safety Monitoring Committee
SO	Safety Officer
UK	United Kingdom
UP	Unanticipated Problem
URL	Uniform Resource Locator
US	United States

10.4 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale
1.0	01-14-2021	N/A; First version	
2.0	07-28-2021	Updates to: 1) study design and statistical analysis plan; 2) Intervention components; 3) risk stratification	In response to the Covid pandemic, we had to change the study design from a randomized trial to a non-randomized quasi-experimental design; 2) We adapted the intervention materials in response to clinician request, including live webinars (rather than just pre-recorded); 3) Updated risk stratification/exclusions based on clinician feedback
3.0		Updates to: 1) Patient eligibility window; 2) Recruitment timeline; 3) Power and statistical analysis	Impacts from COVID have resulted in fewer early stage breast cancer and CRC patients diagnosed at early stage during

			2020-2021, necessitating changes to our eligibility and power/analysis plan; COVID has also impacted clinical staff availability, necessitating a longer recruitment timeline

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