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Assessing Effectiveness and Implementation of an EHR Tool to Assess Heart Health Among Survivors (AH-HA)

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No participant accruals occur at this site
¥ Wake Forest Baptist Comprehensive Cancer Center Qualitative and Patient-Reported Outcomes will conduct all interviews for non-patient participants through NC002.

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Amendment 4	Version 08/13/2021	Released 09/02/2021
Amendment 5	Version 02/10/2022	Released 04/26/2022

Site Participation will be limited to Wake Forest NCORP Components and Sub-components who meet the site eligibility and are randomized using the methods presented in the protocol.

CONTACT INFORMATION		
For regulatory requirements:	**For patient enrollments:**	**For data submission:**
Regulatory documentation must be submitted to the Cancer Trials Support Unit (CTSU) via the Regulatory Submission Portal. (Sign in at https://www.ctsu.org, and select the Regulatory > Regulatory Submission.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-CTSU (2878) for regulatory assistance.	Refer to the Participant Enrollment section for instructions on using the Oncology Patient Enrollment Network (OPEN). OPEN is accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions by phone or email: 1-888-823-5923, or ctsucontact@westat.com.	Data collection for this study will be done through REDCap. Refer to the data submission section of the protocol for further instructions. Address: Wake Forest NCORP Research Base Wake Forest Baptist Medical Center Building 525@Vine, 4th floor Medical Center Boulevard Winston-Salem, NC 27157 Fax: (336) 713-6476 Email: NCORP@wakehealth.edu Do **not** submit study data or forms to CTSU Data Operations. Do **not** copy the CTSU on data submissions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific page of the CTSU members' website (https://www.ctsu.org). Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password.		
For clinical questions (i.e. patient eligibility or treatment-related) contact Wake Forest NCORP Research Base (WF NCORP RB) at NCORP@wakehealth.edu. All correspondence will be triaged to the appropriate WF NCORP RB representative.		
For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) Contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Website is located at https://www.ctsu.org.		

SCHEMA

Study Population: Breast, prostate, colorectal, endometrial, or Hodgkin and non-Hodgkin lymphoma cancer survivors presenting to 8-12 NCORP practices for post-treatment follow-up care

↓

Randomization: 1:1 practice level randomization (4-6 intervention, 4-6 usual care)

↓

Intervention: Implementation of the Automated Heart-Health Assessment (AH-HA) EHR cardiovascular health (CVH) assessment tool and provider education sessions

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Data Collection from Survivors: Baseline (pre & post-visit), 6 months, and 1 year- demographics, referrals to health services (including primary care and cardiology), CVH discussions, cardiovascular risk factor data

Data Collection from Key Informants: **(**after 30 patients are enrolled and 4 weeks after AH-HA Implementation) Semi-structured interviews assessing perceptions and perceived impact of the AH-HA tool on practices, providers, and survivors; barriers and facilitators to implementing AH-HA into practice; and suggested changes to AH-HA to improve future adoption, implementation, and maintenance.

↓

Primary Endpoint: Cardiovascular health discussions defined as patient-reported discussions with their provider for up to seven non-ideal CVH conditions identified for that patient. Conditions include CVH factors (cholesterol, blood pressure, glucose/hemoglobin A1c) and CVH behaviors (body mass index, smoking, diet, and physical activity).

Study Sample**:** n=560-700 survivors of breast, prostate, colorectal, endometrial cancers; or Hodgkin and non-Hodgkin lymphomas; n=38-42 key informants.
Study Duration**:** 1 year

Brief Eligibility Criteria**:**

Practices*:* (1) use of the Epic© EHR, (2) willingness to incorporate the AH-HA tool in their EHR, (3) have two or more providers willing to be trained and use AH-HA, and (4) identified providers saw ≥100 potentially eligible patients (combined total for all providers) for follow-up in prior 6 months.

Survivors*:*
(1) ≥ 6 months post-potentially curative cancer treatment for breast, prostate, colorectal, endometrial cancers, or Hodgkin and non-Hodgkin lymphomas. Ongoing hormonal therapies such as tamoxifen, aromatase inhibitors (with or without adjuvant CDK 4/6 inhibitors such as abemaciclib), or androgen deprivation are allowed.
(2) Scheduled for a routine cancer-related follow-up care visit for one of the cancer types listed above with an identified AH-HA provider.
(3) Able and willing to complete a follow-up assessment in one year;
(4) No evidence of disease at the time of last medical visit for all cancers, except non-melanoma skin disease.

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1. OBJECTIVES

The *objective of this hybrid effectiveness-implementation study* is to examine the effects of the AH-HA tool among breast, prostate, colorectal, endometrial, and Hodgkin and non-Hodgkin lymphoma cancer survivors (N=560-700) receiving survivorship care in community oncology practices, using a group-randomized trial design (4-6 intervention practices and 4-6 usual care practices). Our *central hypothesis* is that the AH-HA tool will increase (1) cardiovascular health (CVH) discussions among survivors and oncology providers, (2) referrals and visits to primary care and cardiology (care coordination), and (3) cardiovascular (CV) risk reduction and health promotion activities compared to usual care.

1.1 Primary Objective

Assess the impact of the AH-HA tool on providers' efforts to discuss CVH during visits as compared to usual care. Cardiovascular health discussions will be defined as patient-reported discussions with their provider for any of the seven non-ideal CVH conditions identified for that patient. Conditions include CVH factors (cholesterol, blood pressure, glucose/hemoglobin A1c) and CVH behaviors (body mass index, smoking, diet, and physical activity).

1.2 Secondary Objectives

1.2.1 Assess the impact of the AH-HA tool on providers' efforts to: (1) refer survivors to primary care and cardiology, and (2) manage CV risk (ordering of CVH-relevant labs and treatments), using data from survivor (N=560-700) reports and the EHR at baseline, 6 months, and one year after enrollment.

1.2.2 Measure the impact of the AH-HA tool on survivors': (1) completed visits with primary care providers and cardiologists, (2) control of CVH factors (cholesterol, blood pressure, glucose/hemoglobin A1c) and CVH behaviors (body mass index, smoking, diet, and physical activity), (3) perception of CV risk and knowledge of CVH factors, and 4) satisfaction with care using data from survivor (N=560-700) reports and the EHR at baseline, six months, and one year after enrollment.

1.2.3 Examine factors influencing current and future implementation of the AH-HA tool. 1) Assess *Reach* of the AH-HA tool in community oncology practices using EHR data (proportion and characteristics of survivors for whom AH-HA is utilized in clinic) and 2) identify potential barriers and facilitators to "real-world" delivery of the intervention and ascertain potential modifications to maximize *Adoption, Implementation,* and *Maintenance* by collecting data from providers and practice administrative leaders via semi-structured interviews.

2. BACKGROUND

2.1 Cardiovascular Health among Survivors

Evidence and Opportunity: Survivors of many common early-stage cancers are now more likely to die of cardiovascular (CV) disease than cancer, elevating the importance of addressing cardiovascular health (CVH) in routine survivorship care.[1-5] Over 90% of survivors have multiple CV risk factors,[6] increasing their risk of both poor CV and cancer outcomes.[7-15] Contributors to heightened CV risk among cancer survivors include: (1) shared mechanisms between cancer and CV disease, including inflammation, tobacco, and obesity,[7, 16] (2) adverse changes in lifestyle factors during cancer treatment (e.g., weight gain),[17, 18] and (3) cardiotoxic effects of certain cancer treatments.[1, 19]

Burden of CV Risk Factors among Survivors: Few adults (<1%) report ideal CVH,[7, 8, 20-22] and cancer survivors are no exception.[23] Fewer than 17% of cancer survivors are non-smokers, exercise, and have a healthy weight.[24] Over 85% of survivors do not meet the American Heart Association's (AHA's) healthy standards in multiple CVH components [body mass index (BMI), physical activity, diet, smoking, blood pressure, cholesterol, and glucose].[6, 25] Underserved (e.g., racial/ethnic minority or low income) survivors may have heightened risk.[26-29] Important risk factors – physical inactivity, unhealthy diet, obesity, and smoking – are common to CV disease and cancer.[7, 30]

Cardiotoxic Effects of Cancer Treatment: Common treatments, including chemotherapies (e.g., anthracyclines),[31-38] trastuzumab,[35, 39] hormonal treatments,[40-42] and radiation[38, 43, 44] are linked with CV injury,[1, 24] further increasing CV disease susceptibility among cancer survivors.[19, 42, 45] Cancer treatment and recovery can also cause weight gain and decreased physical activity, increasing CV disease risk.[19, 46] Addressing CVH is critical for all cancer survivors, especially those who receive cardiotoxic treatments, to mitigate CV-related outcomes.[19, 38, 47, 48]

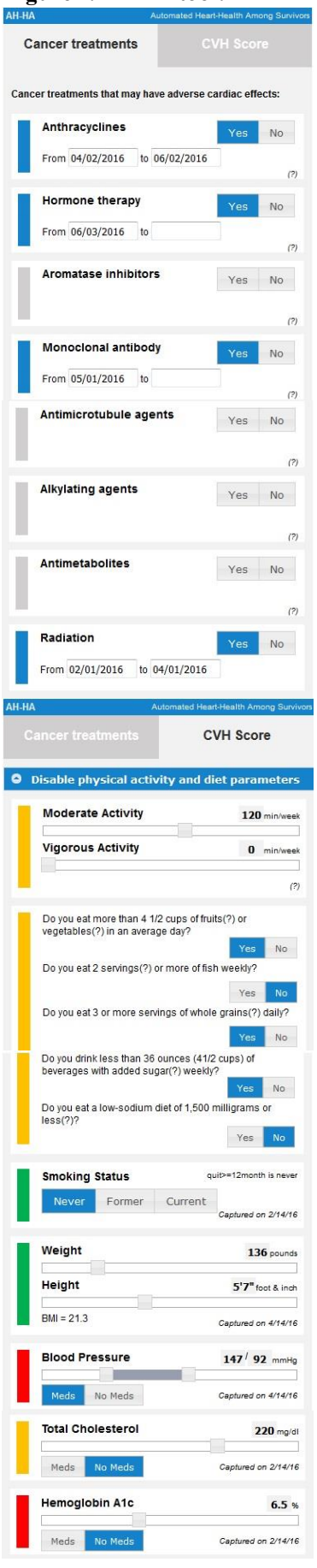
CVH is Under-Addressed among Cancer Survivors:[26, 49] Despite Institute of Medicine (IOM) recommendations for prevention efforts and care coordination for cancer survivors,[50-52] up to 20% of breast and colorectal survivors may not see a primary care provider,[53, 54] heightening their risk for lack of preventive services and poor comorbidity management.[54-56] Claims data reveal that only 31-39% of breast cancer survivors received cholesterol screening, significantly fewer than matched women without breast cancer.[56] Ninety percent of oncologists in our pilot study (18 of 20) reported CVH discussions to be "somewhat" or "very" important; however, 58% "rarely" or "sometimes" discuss CVH with their patients. As a result, oncologists make few referrals for CV care to primary care and cardiology for guideline-driven follow-up care.[25, 49, 57, 58] Nearly 35% of cancer survivors do not receive assistance from a healthcare provider for lifestyle change.[3]

Need for Improved CV Management: Better CVH among survivors improves survival[59] and lowers risk of CV disease[47, 60, 61] and cancer recurrence.[11-15] Increases in CVH correspond to lower risk of mortality (all-cause,[62, 63] CV disease,[62, 63] and cancer[63]), and incident CV disease,[64] stroke,[10] and cancer.[7, 9, 65] Appropriate management of obesity,[66, 67] physical activity,[68] diet,[68, 69] blood pressure,[30] smoking, and diabetes[30] can favorably impact recurrence and overall survival in cancer patients.[70] Survivors who follow-up with primary care providers are more likely to have preventative discussions[71] and improved CVH monitoring;[72] yet only 28% receive follow-up care from both a primary care provider and oncologist.[57] Survivors seen by cardiologists in specialized CV prevention clinics have also seen improvements in cholesterol and blood pressure.[60]

2.2 The AH-HA Intervention

Impact of Clinical Decision Support Targeting CV-specific Risk is Unknown: EHR-based tools can prompt smoking cessation counseling and

Figure 1. AH-HA tool.[26]



referrals,[73] facilitate goal-setting among pre-diabetic individuals,[74] lower cholesterol,[75] improve BMI and diabetes status,[76] and increase appropriate prescribing.[77] Improved patient outcomes through implementation of EHR tools are seen in cardiothoracic surgery[78] and primary care.[76] Available EHR-based tools target individual risk factors (e.g., smoking,[73] cholesterol[75]) or specific diseases (e.g., diabetes,[74] HIV[79]). None integrate multiple, complementary health behaviors and factors at the point-of-care. CV risk factors rarely occur in isolation.[80] Automated clinical decision support tools could increase provider adherence to clinical guidelines[81] and IOM recommendations,[50] but have not been tested for CVH in cancer survivorship care.[82]

The Automated Heart-Health Assessment (AH-HA) Tool Addresses the Complex CVH Needs of Survivors: (**Figure 1**) Our team developed and deployed a novel, easy-to-use, EHR-embedded CVH assessment tool that renders a *visual, interactive display* of CVH risk factors, automatically populated from the EHR.[76, 83, 84] This tool was first implemented in primary care and now incorporates EHR data on receipt of cancer treatments with cardiotoxic potential. We propose to test and evaluate AH-HA in a new setting – survivorship care – and expect high rates of usability in our intervention practices given our feedback so far from oncologists, cardiologists, and survivors during tool redesign and preliminary testing.

Our State-of-the-art AH-HA Tool Can be Easily Implemented into Clinical Practice and Widely Disseminated.[85] We designed the AH-HA tool with a multidisciplinary team to integrate seamlessly into provider workflow, unlike other EHR-based clinical decision support systems. AH-HA could revolutionize survivorship care by allowing an oncologist to quickly: assess survivor CVH (traditional CV risk factors and receipt of potentially cardiotoxic treatments) and coordinate appropriate care. We will update AH-HA with short- and long-term cardiotoxicity and/or CV risk algorithms, as data become available, and can integrate clinical practice guidelines as these are developed.

Clinical Decision Support Tools Continue to Evolve.[86] Our AH-HA tool has been tested for ease of use in busy practices and facilitates discussions to address CV risk issues. It is also more comprehensive and less obtrusive than previous tools. While we will rely on rigorous, tested methodologies to test the effectiveness of the AH-HA tool, our emphasis on qualitatively and quantitatively characterizing the *reach*, *adoption*, *implementation*, and *maintenance* of AH-HA will produce novel data to enhance generalizability of our findings beyond this specific tool and setting.[87] By simultaneously collecting novel data on barriers and facilitators to "real-world" implementation, we will inform efforts to disseminate the AH-HA tool and efforts to implement other EHR-integrated health assessment/risk tools within community oncology practices in a standards-compliant EHR environment.

2.3 Rationale

Awareness of CVH Can Favorably Change Health Behaviors and CVH Management:[88, 89] Data from our team and others show that survivors want to have preventative discussions with their oncologists.[26] Although some oncology providers are hesitant to address obesity and exercise in cancer survivors,[90] exercise recommendations by providers increase cancer survivors' physical activity by up to 30 minutes per week.[91, 92] Behavioral interventions for weight loss,[93] exercise,[94] diet,[95] and smoking cessation[96] – even if brief[97] – can be successful in improving CVH among cancer survivors.[46] For example, the odds of abstinence from smoking at 6 months increased 66% with provider lifestyle advice.[97] Our preliminary data from an EHR-based intervention in primary care show improvements in BMI and diabetes at one year.[76]

Focus on the Advancement of Connected Health for Cancer: We address the three high-priority research areas identified by the President's Cancer Panel to advance connected health for cancer: (1) Improve understanding of how connected health can enable effective teamwork in healthcare, (2) Identify strategies to enhance individuals' engagement in their healthcare, and (3) Develop approaches for using data from connected devices in meaningful ways to enhance clinical care.[98] Pilot studies of single-practice tool

implementation demonstrate improvement in patients' CVH.[76] However, less-studied are practice-, provider-, and patient-level factors that may adversely affect intervention fidelity within and across practices. A paucity of data exists relative to technology adoption and usage in community practice settings,[86] and we lack best practices for tool implementation in community settings. Careful implementation and monitoring are needed to ensure that such healthcare innovations do not exacerbate disparities in care coordination and CVH awareness and outcomes for underserved patients.[99,100]

Survivorship Care is an Optimal Time to Address CVH: Our preliminary data indicate that cancer survivors have substantial room for improvement in CVH, and the use of our adapted EHR tool is supported by survivors and their providers. If successful, the proposed study will generate excellent data to guide future AH-HA tool dissemination efforts. We hypothesize that care coordination and awareness of CV disease risk are important factors. Our ultimate goal is to improve CVH among the rapidly growing population of cancer survivors, currently estimated to be 15.5 million.[101] Use of the established NCORP network is efficient and provides an excellent opportunity to test our intervention in community oncology settings, where most cancer survivors receive care.

Preliminary Data: Our team has extensive, collaborative experience in evaluating the burden of CV risk factors among cancer survivors, conducting usability and implementation studies for clinical decision support interventions and NCORP feasibility studies.

- **Prevalence of Adverse CVH is High among Cancer Survivors:** We analyzed data from the NCI Follow-Up Care Use among Survivors (FOCUS) Study to characterize the prevalence of CVH and preventive health discussions with healthcare providers. Among 5- to 10- year survivors of breast, prostate, colorectal and gynecologic cancers (N=1490), 35% reported a history of CV disease. Except for current smoking, CV risk factors were more common among cancer survivors than adults in general. Of survivors, 62% were overweight or obese, 55% were hypertensive, 21% had diabetes, 18% were physically inactive, and 5% were current smokers.[25] Among survivors with one or more risk factors for CV disease, 33% did not report a health promotion discussion with their healthcare providers. Few (14%) long-term survivors reported referral to a cardiologist (6% of those without a history of CV disease and 29% of those with a CV disease history, $p<.0001$).[25]

- **Successful Tool Integration in Primary Care:** Dr. Foraker developed and implemented the original AH-HA tool, and tested it for a year among 41 urban primary care providers whose patients are of low socio-economic status.[84] Providers reported high usability and acceptability within the EHR-evaluation domains of content, accuracy, format, ease of use, and timeliness.[102] Duration of tool use during an appointment was under 3 minutes, and over the test period, there were 390 tool views for 410 eligible patients.[102] The proportion of obese patients decreased from 47% to 43%, and the proportion of normal-weight patients increased from 15% to 19% (average weight loss: 2.7 kg).[102] Thus, the tool was used by busy primary care providers, and suggested effectiveness in improving patients' risk factors for CV disease.

- **CVH is Overlooked in Cancer Survivorship Care:** In our prior studies with oncologists and survivors, both consider CVH to be important to address, but is frequently overlooked during post-treatment survivorship care.[20-22] Up to 20% of survivors do not receive primary care services, placing them at high risk of missed preventive care opportunities and highlighting the need for improved care coordination.[23,24]

- **Acceptability among Oncology Providers and Survivors.** Drs. Weaver and Foraker conducted one-on-one interviews with 14 oncologists within NCORP practices to assess their attitudes and beliefs toward the original AH-HA tool.[115] Next, they assembled a clinical advisory group of

oncologists and cardiologists to redesign the original AH-HA tool for use in survivorship clinics. Based on data from systematic reviews[11,36,46,100] and expert consensus, eight categories of potentially cardiotoxic treatment categories were incorporated.[1,41,58,114] They then tested the prototype (**Figure 1**) among survivors (N=39) and oncology providers (N=20) to gather data regarding usability and acceptability of the enhanced AH-HA tool. Collectively, these data indicate high acceptability of the adapted AH-HA tool among survivors and oncology providers.

Preliminary Data from NCORP: There are 42 NCORP and minority-based NCORP community members affiliated with the WF NCORP, totaling about 973 individual affiliates/sub-affiliates overall. WF NCORP-affiliated sites are located in 40 states and Puerto Rico and Guam. Since 1999, WF NCORP (previously named Wake Forest CCOP) has recruited 4,557 cancer survivors to clinical studies; 33% were racial/ethnic minorities as well as 68% women, 14% rural residents and 26% age 65 or greater. In 2015 and 2017, we surveyed NCORP practice groups participating in cancer care delivery research (CCDR) and obtained response rates of 87% and 73%, respectively. In the 2017 survey, 94% of practice groups reported having an outpatient EHR. Epic© is the most common system, used by 47% of practice groups with an EHR.

3. SUMMARY OF STUDY PLAN

In this **hybrid effectiveness-implementation group-randomized clinical trial**, 4-6 intervention practices will receive the AH-HA tool and 4-6 practices will serve as usual care (control) practices without access to the AH-HA tool. Providers at each intervention site will be trained to use the tool during routine follow-up care with survivors. Enrolled survivors with breast, prostate, colorectal, endometrial, or Hodgkin and non-Hodgkin lymphoma cancer (N=560-700) will provide baseline data before and immediately after seeing their oncology provider and complete 6-month and 1-year study follow-up visits. We will compare changes in outcomes from baseline to 1-year in survivors at the intervention and usual care clinics using data from survivor self-reports and the EHR. The primary outcome is CVH discussions defined as the number of patient-reported discussions with their provider regarding up to seven non-ideal CVH conditions identified for that patient during oncology visits. Secondary outcomes include referrals to primary care and cardiology, provider efforts to manage CV risk, survivors' completed visits with primary care providers and cardiologists, and control of CVH factors and behaviors. Implementation metrics will be assessed using data from the EHR, structured assessments of usability from providers, and semi-structured interviews with providers and administrators (n=38-42) at intervention clinics.

4. STUDY PRACTICE SITE AND PARTICIPANT SELECTION

4.1 NCORP Practice Inclusion Criteria

Figure 2 describes the recruitment of NCORP practices. A recruitment e-mail ***(Site Invitation to Participate)*** and link to an online ***Preliminary Site Eligibility Screener*** will be sent to the CCDR Leads and PIs of all NCORP community and minority underserved community sites affiliated with the Wake Forest NCORP Research Base. CCDR leads or designees will be asked to provide basic information about all affiliates/sub-affiliates considered or that will be considered for participation. Detailed study information will be provided through e-mails, calls, and webinars, as well as follow-up information technology (IT) calls with NCORP practice personnel when necessary. Each affiliate/sub-affiliate that is interested in participating will complete the ***Pre-Randomization Site Checklist***, including the submission of a ***Site IT Capacity Letter***. CCDR leads at each NCORP site will be asked to rank order their eligible practices in preference of participation. The study investigators will select a practice from each NCORP site to participate.

The unit of randomization is the NCORP practice (which may comprise one or more affiliates/sub-affiliates and must have a single EPIC EHR accessible to all enrolling oncology providers). The Research Base will

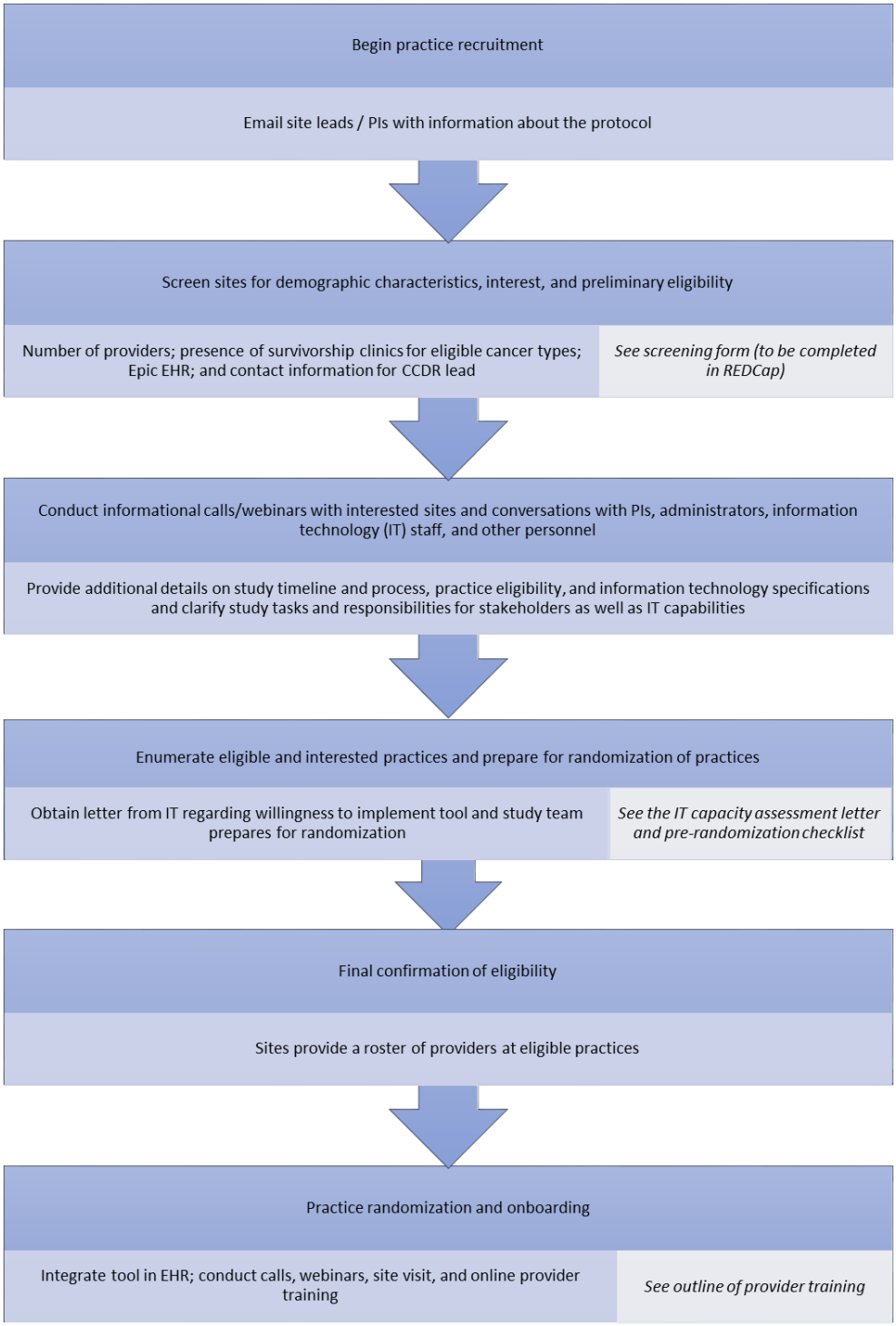
randomize the eligible practices with a 1:1 allocation. Selected practices may not share clinical personnel or EHRs with another participating practice. Practices will be provided with $7,000 in study funds to support recruitment and other activities.

NCORP practice inclusion criteria include:

- use of the Epic© EHR
- willingness to incorporate the AH-HA tool in their EHR
- have two or more providers willing to be trained and use AH-HA
- identified providers saw ≥100 potentially eligible patients (combined total for all providers) for follow-up in prior 6 months

Virtual designated AH-HA appointments are allowed if the site is equipped with a teleconferencing platform and if the participant's survivorship care visit is already scheduled as a virtual visit. For intervention sites, the teleconferencing platform must allow the provider to share his/her screen with the survivor in order to show the AH-HA tool in the EHR. Please see Appendix A for details related to virtual visits.

Figure 2. Practice Recruitment Schema



4.2 Survivor Inclusion Criteria

4.2.1 ≥ 6 months post-potentially curative cancer treatment for breast, prostate, colorectal, or endometrial cancers or Hodgkin and non-Hodgkin lymphomas. Ongoing hormonal therapies such as tamoxifen, aromatase inhibitors (with or without adjuvant CDK 4/6 inhibitors such as abemaciclib), or androgen deprivation are allowed.

4.2.2 Scheduled for a routine cancer-related follow-up care visit (for one of the cancer types listed in 4.2.1) within the next 30 days with a provider participating in the study (in the intervention arm, this is a provider who received training to use AH-HA).

4.2.3 Able and willing to complete a follow-up assessment in one year.

4.2.4 Survivors must have no evidence of disease at the time of last medical visit for all cancers, except non-melanoma skin disease.

4.2.5 Age ≥18 years.

4.2.6 Able to understand and willing to provide verbal informed consent.

4.3 Survivor Exclusion Criteria

4.3.1 Survivors will be excluded if they have a history of cancer recurrence for any cancer other than non-melanoma skin disease.

4.3.2 Prostate patients on active surveillance will be excluded.

4.3.3 Survivor does not speak English or Spanish.

4.3.4. Survivors who are currently on another interventional protocol in which cardiovascular risk factors (e.g., blood pressure, smoking, diet, physical activity) are being addressed, as per patient self-report or research staff members' knowledge at the time of consent.

4.4 Rationale for Cancer Type Inclusion

We focus on these cancer types (breast, prostate, colorectal, endometrial, Hodgkin and non-Hodgkin lymphomas) because they are common prevalent cancers in the United States survivor population that also have an overall 5-year survival that exceeds 50%.[103] In addition, potentially cardiotoxic chemotherapy is commonly received by these survivors and CV disease is a significant competing cause of death for early stage patients with these cancer types.[1-5] Survivors with these types of cancer are also likely to receive at least some of their care in community settings and are likely to benefit from survivorship care post-treatment.

4.5 Recruitment and Retention Plan

Local NCORP site staff will obtain information on follow-up care appointments for survivors of breast, prostate, colorectal, endometrial, or Hodgkin and non-Hodgkin lymphoma cancers. We are requesting a waiver of consent to screen clinical schedules of participating practices and review medical records to identify potentially eligible participants to contact about participating in the study. This process presents no more than minimal risks of harm to the subjects.

Local NCORP site staff are encouraged to contact potentially eligible survivors prior to their appointment via mail, telephone, e-mail, patient portals, or other channels to provide study information, screen, and ascertain interest in participating. Screening can also take place in the clinic on the day of the appointment. A sample ***Survivor Recruitment Phone Script, Letter and Flyer*** are provided. An ***Informational Flyer*** entitled *Cardiovascular Health Study for Cancer Survivors*, should be provided to all patients, regardless of study participation, seeing an AH-HA trained provider in settings where the best practice alert might be activated and used during the visit, regardless of whether or not they have been recruited for the study. The purpose of this flyer is to inform patients at practices randomized to the AH-HA intervention that the practice is participating in a trial.

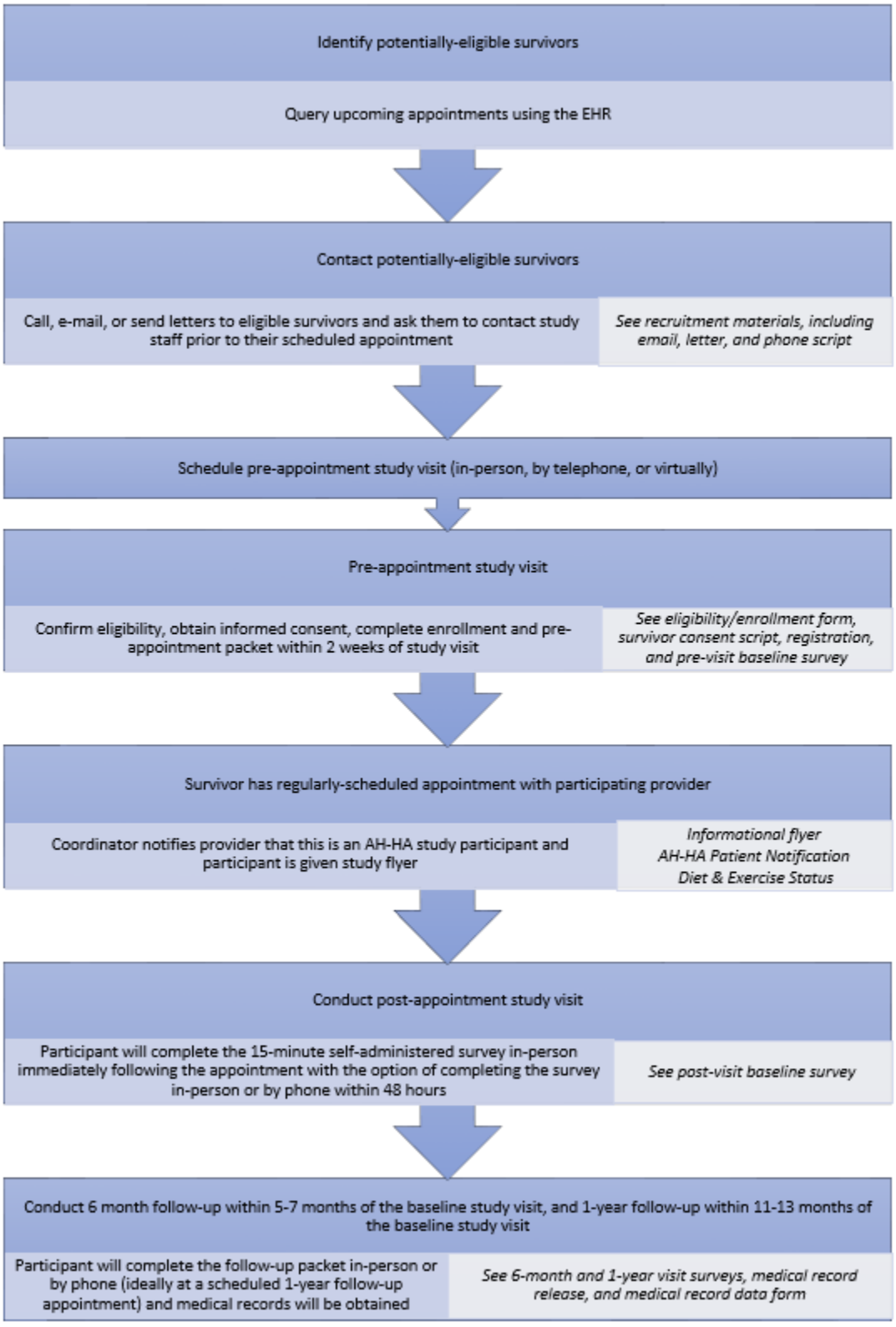
The site coordinator will invite eligible survivors to participate in the research study, administer informed consent, and conduct the ***Pre-visit Baseline Survivor Survey*** (~15-20 minutes) before the visit with the provider. We will track numbers of individuals approached and screened and reasons for nonparticipation. Participants will be allowed to withdraw from the study at any time. A Survivor Recruitment & Intervention Scheme can be found in Figure 3. Finally, Table 1 below reflects the anticipated number of survivor participants enrolled at baseline.

Table 1. Planned Enrollment Report for Patients

Racial Categories	Not Hispanic or Latino: Female	Not Hispanic or Latino: Male	Hispanic or Latino: Female	Hispanic or Latino: Male	Total
American Indian/Alaska Native	2	1	0	0	3
Asian	12	1	0	0	13
Native Hawaiian or Other Pacific Islander	1	1	0	0	2
Black or African American	49	21	0	0	70
White	360	218	21	7	606
More Than One Race	2	4	0	0	6
Total	426	246	21	7	700

Accrual Rate: ___8__ pts/month Total Expected Accrual: __560___ Min __700_ Max

Figure 3. Survivor Recruitment & Intervention Schema



4.6 Patients: Inclusion of Racial/Ethnic Minorities

We will encourage participating practices to approach all potentially eligible survivors, regardless of gender or race/ethnicity. All survivor surveys will be available in English and Spanish. All Minority-Underserved NCORPs affiliated with the Wake Forest NCORP Research Base (WF NCORP RB) will be informed of the study and will be invited to participate. We will emphasize the importance of robust minority accrual at our study kickoff meetings and provide specific education and discussion about strategies to overcome barriers that underserved patients may experience to study participation. Leaders of the Wake Forest Baptist Comprehensive Cancer Center Office of Cancer Health Equity will facilitate this aspect of training and have provided feedback on our recruitment strategy. We will also ask participating Minority-Underserved NCORPs to provide suggestions about strategies for approaching and consenting racial/ethnic minority patients. We will monitor minority recruitment rates at our monthly WF NCORP RB committee meetings and provide feedback to the NCORP sites via bi-monthly study teleconference calls. Specifically, we will monitor the minority recruitment rate in conjunction with available data about the population of survivors to identify sites that are potentially under and over performing with regards to minority accrual. Sites with strong minority recruitment will be asked to share their experiences with other sites during these calls.

4.7 Key Informant Inclusion Criteria (Intervention Practice Sites Only)

4.7.1 Age ≥18 years

4.7.2 Health care provider who completed the AH-HA provider training (e.g., physicians, nurse practitioners, physician assistants) AND

Two members of the site administrative team who participated in the implementation of the AH-HA tool. This will include clinic administrators and/or information technology specialists and is likely to include: facility program directors and other staff (e.g., technology support). Coordinators of centralized services for EHR maintenance at the practice would also be eligible.

4.7.3 Agrees to participate in a confidential 1-on-1 semi-structured interview with the research team.

4.7.4 Agrees to have the interview taped, transcribed and qualitatively analyzed.

4.8 Key Informant Recruitment and Retention Strategy (Intervention Practice Sites Only)

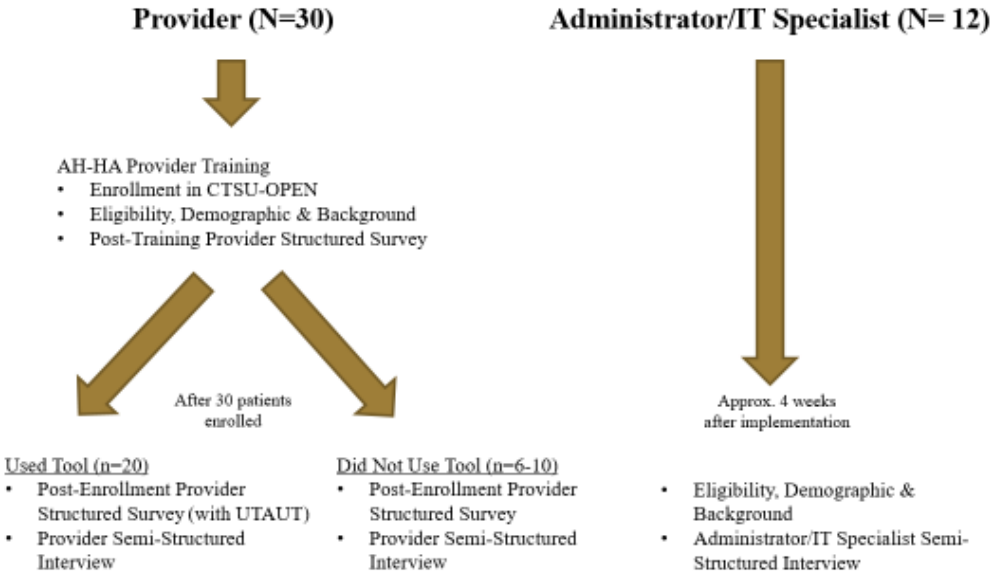
The provider key informant assessment consists of two parts: 1) brief structured surveys at training and after 30 patients are enrolled at the practice and 2) semi-structured interviews for a subset after 30 patients are enrolled at the practice. For more details on the key informant assessments, see Section 6.5: Key Informant Schedule of Events. All providers who complete the AH-HA training webinar (see ***Provider Training Outline***) will have their attendance tracked and recorded. They will be approached for enrollment as key informants via a ***Provider Key Informant Recruitment Email*** sent by the WF NCORP RB. Provider key informants will be enrolled by the site provide their consent in REDCap by proceeding to the post-training survey questions. We anticipate that up to 30 providers may complete the structured surveys.

Provider semi-structured interviews will be conducted by telephone after 30 patients are enrolled at a participating intervention practice. All providers will be identified via the process described above. If more providers completed training and meet these criteria, we will randomly select providers to complete the semi-structured interview. These provider key informants who have not already consented via the process describe above will be sent a ***Provider Key Informant Recruitment Email*** by the Wake Forest NCORP RB.

The administrator/IT specialist key informant assessment consists of one semi-structured interview conducted by telephone approximately 4 weeks after the tool is implemented in the clinic. NCORP site personnel will work with the Wake Forest NCORP research team to identify two administrator/IT specialist key informants within each intervention practice who participated in the AH-HA implementation process. These key informants will be enrolled by the site provide their consent in REDCap by proceeding to the ***Eligibility, Demographic, & Background*** questions.

We anticipate conducting up to 42 key informant semi-structured interviews. The distribution of key informants includes: up to 20 AH-HA trained providers who used the tool with at least two patients (enrolled or not enrolled), up to 10 AH-HA trained providers who used the tool with less than two patients (enrolled or not enrolled), and 12 administrators/IT specialists. See Figure 4 for the distribution of key informants.

Figure 4: Distribution of Key Informants



Key informants will likely be in regular contact with members of the study team as part of the intervention, encouraging their retention.

4.9 Key Informants: Inclusion of Women and Minorities

All nominated key informants, regardless of gender or race/ethnicity will be invited to participate.
Of 42 total key informants, we expect 50% to be women, and 17% to be racial minority. Table 2 below reflects the anticipated number of key informants enrolled at baseline.

Table 2. Planned Enrollment Report for Key Informants

Racial Categories	Not Hispanic or Latino: Female	Not Hispanic or Latino: Male	Hispanic or Latino: Female	Hispanic or Latino: Male	Total
American Indian/Alaska Native	0	0	0	0	0
Asian	4	3	0	0	7
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	1	1	0	0	2
White	16	15	1	1	33
More Than One Race	0	0	0	0	0
Total	21	19	1	1	42

Accrual Rate: _2___ non-patients /month Total Expected Accrual: _38___ Min _42_Max

5. STUDY INTERVENTION

A barrier to efficiently accessing comprehensive and relevant data at the point-of-care is the diffuse presentation of CVH data in the EHR. Vital signs, laboratory results, prescription medications, and health behaviors are captured in multiple discrete fields on distinct screens in the EHR, and are frequently displayed within different activities. We designed the AH-HA tool to aggregate and display data relevant to CVH together, making it easily interpretable for patients and providers alike.

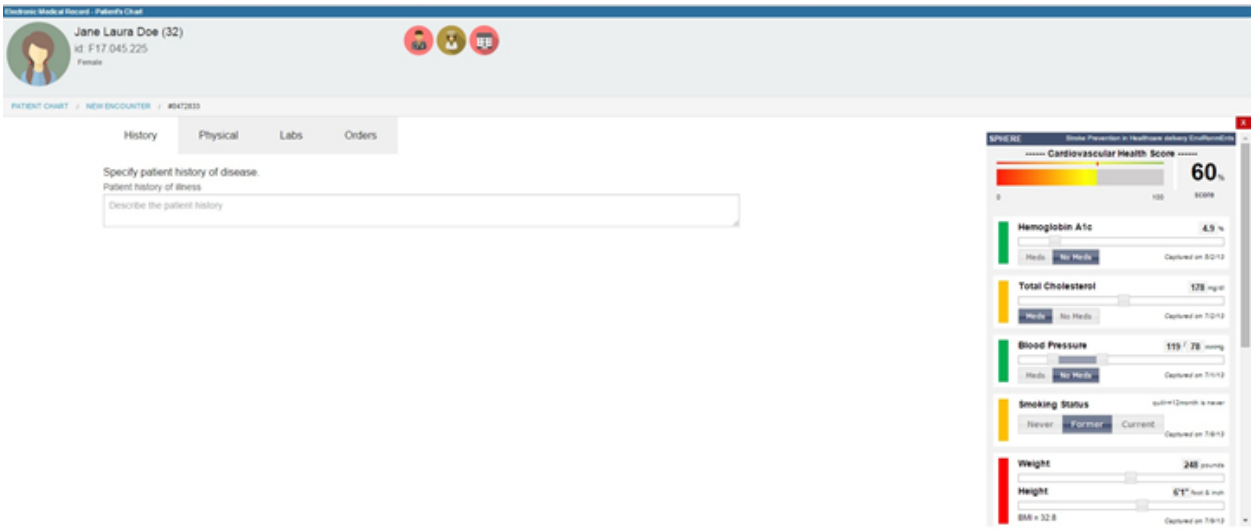
Our AH-HA tool has been tested for ease of use in busy clinics and facilitates discussions to address CV risk issues. It is also more comprehensive and less obtrusive than previous tools. Our study will evaluate "real-world" implementation of healthcare technology in a standards-compliant EHR environment. We successfully launched the original CVH tool in a primary care clinic, within Epic©, one of the most commonly used EHR systems in the United States. The tool has been built to connect with a variety of EHR platforms. We designed the AH-HA tool with a multidisciplinary team to integrate seamlessly into provider workflow, unlike other EHR-based clinical decision support systems.

The AH-HA tool will not replace primary care management of CVH risk factors, intensive behavioral interventions to address weight loss or tobacco use, or specialty management of survivors at high risk for cardiotoxicity, nor does it require oncologists to change their practice to treat CV risk factors. Instead, it will facilitate CVH awareness and action by cancer survivors and their oncology providers. Through systematic assessment of the survivors' CVH needs and triggering referrals, AH-HA will promote care coordination, but more explicit supplemental strategies such as structured information exchange between providers and agreements about managing CVH will likely be needed to optimize CVH care for survivors in community settings.

AH-HA has three features, which leverage existing Epic functionality: (1) on-demand availability via a nondisruptive clinical decision support (CDS) alert; (2) automatic data retrieval for calculations and visualizations; and (3) a nonintrusive view, rendered on a lateral panel that allows concurrent EHR navigation (Figure 5). When the CDS alert is clicked, it triggers existing EHR application programming interfaces (APIs) that collect current encounter parameters for the patient from the vendor's live database,

and delivers them to the AH-HA tool via a secure POST http request. The AH-HA tool then retrieves historical data from the EHR database, and renders the resulting risk-profiling and visualization on an embedded instance of a Web browser engine.

Figure 5. AH-HA tool shown as a lateral panel within the EHR



AH-HA Tool Implementation. A list of topics to be covered in an AH-HA Tool Webinar for interested and enrolled practices is found in the ***AH-HA Tool Information*** document. The AH-HA tool can be programmed to launch for specified users during an encounter with eligible survivors, regardless of study participation; each practice will customize this to fit the needs of their enrolling providers. Extensive training and technical assistance will be provided by the Wake Forest NCORP Study team to ensure successful EHR tool implementation. We will make available an Epic© trained consultant for integration of the tool into the clinic and troubleshooting as necessary. We will also provide tablet technology and support to the clinics to facilitate data entry for survivors and NCORP staff. The study grant can reimburse up to $6,500 for IT services needed for AH-HA implementation, if requested.

Required AH-HA Training for Providers. Practices must identify at least two providers (physicians, nurse practitioners, or physician assistants) who routinely provide post-treatment follow-up care to eligible patients and agree to be trained and use the AH-HA tool. All training will be provided via webinars and teleconferences (see ***Provider Training Outline*** for a list of training topics). Two 30-min AH-HA tool tutorials for all oncology providers who intend to enroll survivors from the 6 intervention clinics will be recorded as webinars and viewed online at a time of the provider's choosing in the month before implementation of the AH-HA tool in the clinic. The provider training will include an ***Epic AH-HA Dot Phrase*** template that providers can use to summarize their cardiovascular health discussion with the patient. It is intended as a guideline and its usage is not required by the study. Completion of the provider training will be tracked centrally by the WF NCORP RB via the ***Provider Training Attestation*** form that providers email after training completion. The educational sessions will review primary prevention of CV disease risk factors according to AHA guidelines for healthcare professionals, cardiotoxicity of cancer treatments, and case-based examples illustrating use of the AH-HA tool in CVH discussions during survivorship care.

6. STUDY EVALUATIONS AND PROCEDURES

6.1 Survivor Schedule of Events

Evaluation of the intervention depends on administration of surveys at baseline pre- and post-visit, 6 month and 1 year after baseline. The ***Survivor Consent Script*** and all surveys will be available in English and Spanish. Sites will mail the consent script to participants who request a copy of the consent information.

SURVIVOR SCHEDULE OF EVENTS

Evaluation	Screening	Baseline Pre-Visit	Baseline Post-Visit	6 Month Visit (±30 days)	1 Year Visit (-30 to + 60 days)
Eligibility	X				
Enrollment in CTSU-OPEN		X			
Reason for Refusal *(if applicable)*	X				
Informed Consent *		X			
Health Assessment *		X ¥	X §	X £	X £
Health Visit Information *		X ¥		X £	X £
Health Knowledge Assessment *		X ¥	X §		
Medical Record Release *(provided by local site)*		X €			
Demographic & Health Behaviors *		X €			
Counseling & Referral Assessment *			X §		
Tool Assessment *†			X §		
Medical Record Data			X		X

* *available in English and Spanish*
§ *preferably completed in-person immediately following visit, but may be completed by telephone within 48 hours of baseline visit*
£ *in-person or by telephone*
† *intervention sites only*
¥ *these 3 surveys should be completed before the visit and are listed in order of priority. If they are not completed before the visit begins, they should be left incomplete and* ***not*** *completed after the visit.*
€ *the Medical Record Release and Demographic & Health Behaviors can be completed before or after the visit.*

6.2 Prior to Enrollment

Local NCORP site staff will screen individuals for eligibility prior to or during a regularly scheduled appointment. If the individual meets all eligibility criteria and agrees to participate, trained NCORP site staff at each NCORP practice site will seek interest and consent the patient. The study has requested a waiver of documentation of consent, so site staff will use the ***Survivor Consent Script*** to document the participant's consent decision. This script will be used whether the participant is consented remotely or in-person (see Appendix A for virtual visit considerations). Consent may be obtained up to two weeks prior to the designated AH-HA appointment. Sites should enroll the participant into CTSU OPEN after the participant is consented. Participants must also sign a medical record release form provided by the local affiliate/sub-affiliate to allow the request of records from providers outside the study site facility.

Participants will be excluded if they do not meet the inclusion/exclusion criteria. Individuals who decline participation will be asked to complete the ***Reason for Refusal Form*** which includes basic demographic information and primary reason for declining study participation. This form will be entered into the REDCap screening project by NCORP site staff.

6.3 Baseline Assessment

The ***Pre-visit Baseline Survivor Survey*** must be completed within two weeks prior to the designated AH-HA routine follow-up care appointment. If the participant is completing this survey by phone or virtually because they are scheduled for a virtual AH-HA appointment, the survey should be given to the participant on the same day that the participant is consented and enrolled. If the participant is scheduled for an in-person AH-HA appointment, they should complete this survey in the clinic just prior to the appointment. The ***Health Assessment***, ***Health Visit Information***, and ***Health Knowledge Assessment*** components should be given in that order during the ***Pre-visit Baseline Survey***. If they are not completed before the visit begins, they should be left incomplete and **not** returned to after the visit. The ***Medical Record Release*** and ***Demographic & Health Behaviors*** can be completed before or after the visit.

For intervention sites only, the local NCORP site coordinator or the participant will fill out the diet and exercise status answers via a paper form (***Diet and Exercise Status)*** and give it to the provider at the beginning of the visit so that the provider can put that information into the AH-HA tool. An ***AH-HA Patient Notification*** sign will be available to sites to alert the provider that the AH-HA tool should be used in this visit for enrolled participants (see Appendix A for virtual visit considerations), but the provider can use the AH-HA tool at his/her discretion with any eligible patient from their clinic. Usual care sites will not alert the provider that the patient is an AH-HA study participant because they will not be using the AH-HA tool.

For intervention and usual care sites, the ***Post-visit Baseline Survivor Survey*** must be completed no more than 48 hours after the designated AH-HA appointment (a maximum of five days from the designated AH-HA appointment is allowed if the participant cannot be reached by the study staff within the first 48 hours). More information on the assessments included in these Baseline Survivor Surveys can be found in Section 6.1. Core measures include: demographics, health status, perceptions of CV risk, and receipt of CVH discussions and referrals. The baseline assessments will be completed in-person (see Appendix A for virtual visit considerations), in conjunction with a regularly scheduled follow-up care visit with a participating provider. In the rare case that an appointment is cancelled after a ***Pre-visit Baseline Survivor Survey*** is completed, this survey does not need to be repeated if the appointment is rescheduled within 7 days. The ***Post-visit Baseline Survivor Survey*** should be completed immediately after the designated AH-HA appointment. In the rare case that a patient does not complete the ***Post-visit Baseline Survey*** on the same day, this survey should be completed in-person or by phone within 48 hours of the designated AH-HA

appointment. All responses will be recorded on paper forms and/or entered directly into the online database. Local NCORP site staff will be responsible for entering the data into REDCap. Local NCORP site staff will also complete the ***Medical Record Data*** form at the post-visit time point.

Participants will receive a $10 gift card when the ***Post-visit Baseline Survivor Survey*** is completed. Electronic gift cards will be sent directly to the patient if the patient provides an email. The Wake Forest NCORP project management team will maintain a log of distributed gift cards. If the patient does not have an email, the electronic card will be sent to the local NCORP site coordinator who will print the card and either mail or give it to the patient in person.

6.4 6 Month and One Year Assessments

Local NCORP site staff will contact each participant to complete a 20-minute survey (in-person or by telephone) six months (±30 days) and one year (-30 to + 60 days) following the baseline clinic visit. This assessment focuses on completed healthcare visits and CVH behaviors and can be found in the ***6 Month Visit Survivor Survey*** and ***1 Year Visit Survivor Survey***, respectively. More information on the assessments included in these Survivor Surveys can be found in Section 6.1. Participants will be offered a $5 electronic gift card for completing each survey. Local NCORP site staff will also complete the ***Medical Record Data*** form at the 1 year time point.

To minimize attrition, local NCORP site staff will mail letters (***Survivor 6 Month & 1 Year Reminder Letter***) to participants 1-2 weeks prior to the six month and one-year follow-up surveys. At least five attempts will be made to reach each participant by phone. As a final step, the team will consider a mailed survey to non-respondents that includes a gift card.

6.5 Key Informant Schedule of Events (Intervention sites only)

Evaluation	Administrator/ IT Specialist	Providers who use AH-HA	Trained, but non-using Providers
Enrollment in CTSU-OPEN	X	X	X
Informed Consent	X	X	X
Eligibility, Demographic & Background	X§	X#	X#
Post-Training Provider Structured Survey		X	X
Post-Enrollment Provider Structured Survey#		X	X
Administrator/IT Specialist Semi-Structured Interview §	X*		
Provider Semi-Structured Interview #		X*	X*
Unified Theory of Acceptance and Use of Technology (UTAUT) Survey €		X	

 # after 30 patients are enrolled in study
§ approximately 4 weeks after implementation

* *Completed by the Wake Forest NCORP and WFBCCC Q-PRO Shared Resource Teams; up to 20 providers who used AH-HA and 10 providers who were trained but did not use AH-HA will complete an interview.*

€ *The UTAUT is part of the provider post-enrollment structured survey, but will only be given to providers who used the tool.*

The key informant assessment for providers consists of: 1) A ***Post-Training Provider Structured Survey*** immediately after training, 2) a ***Post-Enrollment Provider Structured Survey*** and 3) a ***Provider Semi-Structured Interview*** after 30 patients are enrolled at the practice. The key informant assessment for administrators/IT specialists consists of an ***Administrator/IT Specialist Semi-Structured Interview*** approximately 4 weeks after the tool is implemented in the clinic. Research staff with expertise in qualitative data collection from the Wake Forest team and the Wake Forest Baptist Comprehensive Cancer Center Qualitative and Patient-Reported Outcomes (Q-PRO) Shared Resource will conduct one-on-one interviews by telephone with providers and administrators. Interviews will be scheduled by the Wake Forest and Q-PRO teams with assistance from practice site NCORP team members. All providers and key administrators will also be asked to provide basic demographic (age, sex, and race/ethnicity) and practice (years in practice, position title, and discipline) information on the ***Eligibility, Demographic & Background Information*** via a REDCap survey link emailed to them.

The ***Post-Training Provider Survey*** will assess the initial reactions of the providers to the AH-HA tool. Providers will receive a $10 gift card after this survey. They will have the option to decline compensation. The ***Provider Post-Enrollment Structured Survey*** focuses on the feasibility and sustainability of the clinical decision support tool. The performance, effort, attitude, facilitating conditions, and behavioral scales of the ***Unified Theory of Acceptance and Use of Technology (UTAUT) Survey*** will be administered to all AH-HA trained providers who use the tool with patients as part of the ***Provider Post-Enrollment Structured Survey*** to assess factors associated with tool use. The surveys are estimated to take 5 minutes at training completion and post-enrollment.

Administrator/Provider Semi-Structured Interviews will focus on: (a) adoption; (b) implementation; and (c) maintenance of electronic health record-based clinical decision support. Interview topics were guided by the "RE-AIM Checklist for Study or Intervention Planning", "RE-AIM Model Dimension Items Checklist" and the Consolidated Framework for Implementation Research (http://www.cfirguide.org/) and include:[104-106] (1) general perceptions and perceived impact of AH-HA tool on practice, providers, and patients, (2) barriers and facilitators to implementing AH-HA in the practice (emphasizing implementation constructs such as *Perceived Effectiveness, Intervention Characteristics, Adaption, Maintenance, Implementation, Outer Setting, Inner Setting, and Adoption*), and (3) suggested changes to AH-HA to improve future adoption, implementation, and maintenance. Administrator interviews will be conducted approximately 4 weeks after the AH-HA tool has been fully implemented at the intervention practice. Provider interviews will take place after 30 enrollments at the practice.

Administrator/Provider Semi-Structured Interviews will last approximately 30 minutes and be audiotaped; participants will receive a $20 electronic gift card. They will have the option to decline compensation at the end of the interview. Digital recordings of each interview will be independently transcribed verbatim to ensure validity. We will also ask administrators to estimate the time and cost (personnel and other) of AH-HA tool implementation, to include: provider training and AH-HA tool integration into their site.

7. CRITERIA FOR EVALUATION AND ENDPOINT DEFINITION

7.1 Summary Table of Endpoints, Measures, Measurement Strategies, and Time Points

	Measure	**Measurement Strategy**	**Time Point(s)**
Primary Endpoint (Effectiveness, Aim 1)	CVH discussions (at least one non-ideal CVH factor discussed)	Survivor survey (discussions, diet, and primary care); EHR for other CVH factors	Baseline: post-visit
Secondary Endpoints (Effectiveness, Aim 1)	1) Referrals to primary care and cardiology and 2) efforts to manage CV risk (ordering of CVH-relevant labs and treatments)	Medical chart abstraction	1 year
Secondary Endpoints (Effectiveness, Aim 2)	1) Number and date of primary care and cardiology visits in the past year, 2) CVH behaviors (smoking status, BMI, physical activity, and healthy diet) and CVH factors (total cholesterol, blood pressure, and fasting plasma glucose/A1c), 3) perception of CV risk, knowledge of CVH factors, and patient activation, 4) Satisfaction with care	1 & 2) Medical chart abstraction (survivor survey as secondary verification source/ primary for diet and physical activity) 3 & 4) Survivor survey	Baseline; 1 year Baseline: pre & post-visit; 6 mo, & 1 year
Secondary Endpoints (Implementation, Aim 3a)	Proportion and characteristics of survivors for whom AH-HA is utilized in clinic, regardless of enrollment to the study	EHR log data from Clarity Query	1 year
Secondary Endpoints (Implementation Aim 3b)	Barriers and facilitators to the adoption, implementation, and maintenance of the tool in intervention practices Tool acceptability	Key informant interview- including structured survey and semi-structured interviews ***Implementation Time Study Template*** Survivor Surveys	After 30 patients are enrolled (provider) and 4 weeks after implementation (admin/IT) Baseline: post-visit

7.2 Primary Endpoint

Immediately after their survivorship care appointment, at baseline, each survivor will be asked if they were counseled on 10 topics: 7 CVH topics (BMI, physical activity, diet, smoking status, blood pressure, cholesterol, and glucose), and 3 distractor topics (flu vaccination, shingles vaccination, and fall prevention). Questions were adapted from the NCI APECC[107] and FOCUS[25] studies (***Survivor Surveys***). All questions are consistent with prevention services covered by the Affordable Care Act (blood pressure, cholesterol, and diabetes screening; diet counseling; obesity screening and counseling; and tobacco screening and cessation support), and thus have important implications for meaningful use of EHRs.[108] The primary outcome will be the proportion of patients reporting at least one non-ideal or missing CVH topic discussed during the visit.

7.3 Secondary Endpoints

We will also ask survivors about (1) having a primary care provider and cardiologist, (2) the number of visits, and (3) date of last visit to primary care providers and cardiologists in the past year, query the EHR for documentation, and obtain consent to obtain medical records to ascertain out-of-network visits. These data will additionally be used as a stratification variable in exploratory analyses for Aims 1 & 2.

Additional Outcomes of Interest (Aim 1). In addition to the primary endpoint of any discussion of a non-ideal or missing CVH topic, we will summarize the proportion of survivor reported discussions with their provider for each of the 7 non-ideal or missing CVH topics. Additionally, we will summarize for each survivor the proportion of non-ideal topics discussed. We also will review clinic notes from intervention and control clinics to document preventative discussions regarding CVH at each survivor visit that occurs between baseline and follow-up.[128] At baseline and follow-up, survivors will be asked if they received referrals to see a primary care provider and/or a cardiologist (***Survivor Surveys***). We also will review clinic notes to document referrals and communication with other providers regarding CVH at each survivor visit that occurs between baseline and follow-up. We will also document orders for CVH-relevant labs and treatments.[128] Provider orders for total cholesterol and glucose/hemoglobin A1c will be queried according to the methodology of our study of the previous CVH tool.[27,28] Relevant CVH medication data will be abstracted according to previously described methodology, and will include orders for: blood pressure, cholesterol, and diabetes (insulin and pill) medications.[27,28] These laboratory and medication data are input in the "order" screen of the EHR and will be collected for each survivor-provider encounter.

Additional Outcomes of Interest (Aim 2). The 4 CVH behaviors (smoking status, BMI, physical activity, and healthy diet) and 3 CVH factors (total cholesterol, blood pressure, and fasting plasma glucose/A1c) will be collected during usual clinical care, or queried via tablet prior to the survivor's appointment.[84] As physical activity and diet data are not typically stored in the EHR, survivors will be asked to enter these data onto a paper form or into a tablet upon arrival for their scheduled appointment (***Survivor Surveys***). CVH is an evidence-based metric, called "*Life's Simple 7*", which was developed and validated by the AHA in 2010[108] and has been used in more than 100 publications to date. We will categorize each CVH component according to clinical cut-points established by the AHA.[108] At baseline and follow-up, we will also ask survivors about their perception of their CV risk and their knowledge of their CVH factors (***Survivor Surveys***). Health knowledge questions were adapted from a survey assessing the relative risk of cancer and cardiovascular disease in United States populations.[117]

Additional Outcomes of Interest (Aim 3). Quantitative EHR data from system use logs will be used to determine the frequency and duration of use of the AH-HA tool in intervention clinics for Aim 3.[102] We will also capture the number of eligible patient visits, regardless if they were enrolled on the study or not, during which the AH-HA tool was used in intervention clinics and the total number of eligible visits. We will receive these EHR data from intervention sites via a ***Clarity Query*** that includes the data fields outlined

below. Sites will send us a query monthly for audit purposes to ensure functionality of the tool and at the end of year 1 for research purposes (Implementation, Aim 3a). Sites will securely upload the query as a CSV file to an NCORP REDCap project. The primary outcome for these analyses is the ratio of eligible patient visits during which the AH-HA tool was used / total number of eligible visits. The following data will be extracted from the EHR for both enrolled and unenrolled eligible patients: patient (age, sex, race/ethnicity, health insurance type, comorbidities), cancer characteristics (stage and type), cardiovascular health (blood pressure, blood pressure medication, hemoglobin A1C, diabetes medication, total cholesterol, cholesterol medication, BMI, smoking), visit (visit type, reason for visit, time since first visit with a provider in the study, inpatient or outpatient encounter) and AH-HA tool usage (enrolled, mode, alert month, action taken, BPA location, BPA identifier) All patient information will be de-identified before submission to WF NCORP RB, but sites should ensure they are compliant with all local HIPAA policies when gathering the data. Provider data (sex, years in practice, specialty) will be obtained by linking the National Provider Identifier (NPI) from the EHR to the NPI registry (https://npiregistry.cms.hhs.gov/), which discloses these and other provider-level data to the public as part of the Freedom of Information Act.[109] Sites will also complete the ***AH-HA Tool Implementation Time Study Template*** to provide information about the person-hours required for each IT implementation step to determine cost and capacity. This will be completed with the key informant interview 4 weeks after implementation. In the Baseline: Post-Visit Survey, survivors will complete a ***Tool Assessment*** questionnaire assessing whether or not they recall seeing or discussing the AH-HA tool with their provider and five questions assessing: how much they liked the tool, how helpful it was, how easy it was to understand, how much it improved their understanding, and if they would like to use this tool in the future.

7.4 Off-Study Criteria

Participants may go 'off-study' for the following reasons: the protocol intervention and any protocol-required follow-up period is completed, AE/SAE, lost to follow-up, withdraw consent, death, determination of ineligibility.

7.5 Study Termination

NCI, DCP as the study sponsor has the right to discontinue the study at any time.

8. REPORTING ADVERSE EVENTS

This is a group randomized controlled trial with minimal risks. No routine Adverse Events or Serious Adverse Events are reported.

9. STUDY MONITORING

9.1 Data Management

Data management for this study will be done electronically using the following systems.

Participant Enrollment	REDCap/OPEN
Surveys and Data Collection	REDCap

REDCap is a secure, web-based, and easy to program forms and research database platform utilized by the

WF NCORP for many research projects. This study will be using REDCap as the electronic data collection platform including electronic Case Report Form (eCRF) for multi-site studies.

9.2 Case Report Forms

Protocol-specific case report forms (CRFs) will be submitted electronically to the WF NCORP Research Base Data Management Center via OPEN and/or REDCap within 14 days of visit, phone call or time point completion. Refer to the Schedule of Events in Section 6.1 and 6.5, showing the specific forms that are needed for each study visit.

Do not submit study data or forms to CTSU Data Operations.
Do not copy the CTSU on data submissions.

9.3 Source Documents

Source documents are the original signed and dated records of participant information (e.g., the medical record, shadow chart) which may include electronic documents containing all the information related to a participant's protocol participation. Source documents are used to verify the integrity of the study data, to verify participant eligibility, and to verify that mandatory protocol procedures were followed. An investigator and other designated staff are required to prepare and maintain adequate and accurate documentation that records all observations and other data pertinent to the investigation for each individual participating in the study. All data recorded in the research record (including data recorded on CRFs) must originate in the participant's medical record, study record, or other official document sources.

Source documents substantiate CRF information. All participant case records (e.g., flow sheets, clinical records, physician notes, correspondence) must adhere to the following standards:

- Clearly labeled in accordance with HIPAA practices so that they can be associated with a particular participant or PID;
- Legibly written in ink;
- Signed and dated in a real time basis by health care practitioner evaluating or treating the participant; and
- Correction liquid or tape must not be used in source documents or on CRFs.

All laboratory reports, pathology reports, x-rays, imaging study and scans must have:

- Complete identifying information (name and address of the organization performing, analyzing, and/or reporting the results of the test); and
- Range of normal values for each result listed.

9.4 Data and Safety Monitoring Plan

In accordance with the NIH requirement, a Data Safety and Monitoring Plan (DSMP) has been established to guide the oversight of this study in order to ensure the safety of participants and the validity and integrity of the data. This monitoring will be commensurate with minimal risk present to participants.

The Wake Forest NCORP Research Base Data and Safety Monitoring Committee (DSMC) meets monthly to review reportable Adverse Events and Protocol Deviations to identify urgent safety and data concerns that

may affect study safety and data quality. Adverse Event and Protocol Deviation reports are generated by the Wake Forest NCORP Research Base Data Management team. The DSMC consists of members of the Wake Forest NCORP Research Base team including one of the NCORP Research Base Multi-PIs, the Wake Forest NCORP Research Base Administrator, regulatory, and data team members.

The Wake Forest NCORP Research Base Data and Safety Monitoring Board meets every six months to review Wake Forest NCORP Research Base protocols. The Board includes members demonstrating experience and expertise in oncology, biological sciences, biostatistics and ethics. The DSMB report is generated by the Research Base statistician. Areas of review may include the following: Study Objectives; Patient Accrual; Patient Status and Retention; Study Status; Last Contact Status; Patient Compliance; Number of Biopsies/Labs as needed; Patient Characteristics; Summary of Observed Toxicities; Adverse Events; Date, Event briefly described, Relationship to Drug, Arm assigned; Summary of Primary and Secondary Measures.

DSMB Responsibilities: The DSMB reviews accrual information and interim analyses of outcome data and cumulative toxicity data summaries to determine whether:

- the trial should continue as originally designed
- the trial should be changed
- the trial should be terminated
- outcome results should be released prior to the reporting of the study results

Members of this committee as well as the organization statistician will oversee the safety monitoring of the study to ensure that the privacy of all participants in the study is protected; ensure that participants' interests are primary, that is, above the interests of the scientific investigation; and to ensure that all data collection is scrutinized for accuracy, privacy and levels of protection. The committee will perform reviews of the data handling and confidentiality and comply with recommendations to resolve such problems, and maintain written communication of the deliberations and recommendations that arise from their meetings. By examining this information, they will keep abreast of critical issues regarding recruitment and data integrity. Reports of all DSMB meetings and recommendations will be provided to the NCI, CIRB, WF NCORP RB, and participating sites, as requested.

9.5 Protocol Adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by the Study PI and approved by the DCP, CIRB and any other stakeholders, it cannot be implemented. All protocol deviations will be recorded on the **Protocol Deviation Log** in REDCap.

9.6 Sponsor or FDA Monitoring

The NCI, DCP (or their designee) or Wake Forest NCORP Research Base may monitor/audit various aspects of the study. These monitors will be given access to facilities, databases, supplies and records to review and verify data pertinent to the study. This protocol does not include pharmaceuticals or require FDA monitoring.

9.7 Record Retention

CLINICAL RECORDS FOR ALL PARTICIPANTS, INCLUDING CRFS, ALL SOURCE DOCUMENTATION (CONTAINING EVIDENCE TO STUDY ELIGIBILITY, HISTORY AND PHYSICAL FINDINGS, LABORATORY DATA, RESULTS OF CONSULTATIONS, ETC.), AS WELL AS IRB RECORDS AND OTHER REGULATORY DOCUMENTATION WILL BE RETAINED BY THE INVESTIGATOR IN A SECURE STORAGE FACILITY IN COMPLIANCE WITH HEALTH INSURANCE PORTABILITY AND ACCOUNTABILITY ACT (HIPAA), OFFICE OF HUMAN RESEARCH PROTECTIONS (OHRP) AND NCI/DCP REQUIREMENTS, UNLESS THE STANDARD AT THE SITE IS MORE STRINGENT. WAKE FOREST NCORP RESEARCH BASE REQUIRES THE RECORDS TO BE RETAINED FOR AT LEAST 5 YEARS AFTER THE STUDY IS DISCONTINUED AND THEY SHOULD BE NOTIFIED PRIOR TO ANY PLANNED DESTRUCTION OF MATERIAL, UNLESS THE STANDARD AT THE SITE IS MORE STRINGENT. NCI WILL BE NOTIFIED PRIOR TO THE PLANNED DESTRUCTION OF ANY MATERIALS.

10. STATISTICAL CONSIDERATIONS

10.1 Study Design/Description

A group-randomized study design will assess the *effectiveness* of the AH-HA tool on delivery of CVH discussions. and referrals to primary care and cardiology, as well as CVH monitoring and treatment. Six months after AH-HA implementation, qualitative data will be collected from NCORP oncology providers in intervention clinics who completed the AH-HA provider training and key clinic administrators.

10.2 Randomization/Stratification

Randomization will be used to achieve balance on clinic-level characteristics to assess outcomes related to Aim 1 (provider behavior) and Aim 2 (survivor visits and CVH). The pre-randomization eligibility checklist will include organizational characteristics that may influence the adoption and adaptation of electronic health record-based clinical decision support. We will randomize the sites in groups of two to the intervention (n=4-6) or usual care (n=4-6) arms. Our multi-faceted training program targets health care delivery system changes (e.g., providers, clinics); therefore, all patients seeking follow-up services at a single site will be in either the intervention or usual care arm of the RCT. If a practice opts out post-randomization, another practice will be selected from the remaining eligible clinics within the NCORP site or another NCORP site will be added.

10.3 Accrual and Feasibility

With over 973 affiliates/sub-affiliates within the Wake Forest NCORP Research Base network, we do not anticipate having any challenges with accruing 8-12 affiliates/sub-affiliates to participate in this study. In 2015 and 2017, we surveyed NCORP practice groups participating in cancer care delivery research (CCDR) and obtained response rates of 87% and 73%, respectively. In the 2017 survey, 94% of practice groups reported having an outpatient EHR. Epic© is the most common system, used by 47% of practice groups with an EHR. We anticipate screening approximately 1,500 participants from up to 12 clinics in order to enroll a minimum of 280 participants in the intervention and 280 participants in the usual care arms at baseline and expect to retain 80% of baseline participants to participate in the one year telephone survey.[49,50]

10.4 Primary Objective, Endpoint, Analysis Plan

10.4.1 Analysis Plan

Our primary outcome is the delivery of CVH discussions as assessed by patient self-report during the post-appointment survey. This will be quantified as yes if any non-ideal or missing CVH topic or no if nothing was reported as discussed. Participants must complete both parts of the baseline visit (pre and post) to be included in the analysis; otherwise, they will be replaced. Additionally, although we do not anticipate many survivors to present with all ideal CVH factors, any survivor that has no topics needing discussion at time of visit will also be replaced.[108]

A mixed effects logistic regression model will assess the effect of the intervention on delivery of CVH discussions between intervention and usual care clinics. Intervention group will be a fixed effect and the practice will be a random effect. We plan to conduct two specific subgroup analyses, examining the intervention effect stratifying by whether each participant received cardiotoxic treatment as part of their cancer treatment, and whether the participant visited a primary care provider in the year preceding the baseline visit. We will also summarize reported discussions for each of the 7 non-ideal topics as well as the proportion of non-ideal topics discussed for each survivor.

10.4.2 Statistical Power

In a group-randomized trial (GRT), statistical power critically depends on the degree of similarity between individuals from the same group compared to individuals from other groups, commonly summarized via the intraclass correlation coefficient (ICC). Well-powered GRTs are often difficult to design as seemingly small differences in the ICC (moving from 0.01 to 0.05) can have a dramatic effect on power, and because finding estimates of the ICC in the literature is often difficult.[110,111] We expect a low ICC according to those published in the literature,[112] ranging from 0.02 (physical activity) to 0.03 (obesity).[111,113] In addition, Eldridge et al. summarize ICCs from GRTs and indicate a median ICC of 0.04 across 13 GRTs.

Table 3. Average sample size across 12 practices to provide 80% power by ICC and CVH discussion rate.

		p_{AH-HA}					
ICC	p_{UC}	25%	30%	35%	40%	45%	50%
0.03	10%	38	17	10	7	5	4
	15%	NF	58	22	12	8	6
	20%	NF	NF	84	26	14	9
0.04	10%	55	19	11	7	5	4
	15%	NF	109	26	13	8	6
	20%	NF	NF	274	33	16	9
0.05	10%	99	23	12	7	5	4
	15%	NF	1234	33	15	9	6
	20%	NF	NF	NF	45	18	10

p_{AH-HA}=rate of CVH discussion in intervention clinics
p_{UC}=rate of CVH discussion in usual care clinic
NF=Not a feasible design; ICC= intraclass correlation coefficient

In **Table 3**, we summarize the needed sample size per practice for the outcome of delivery of CVH discussions (yes vs no), assuming 6 practices per treatment group, 80% power, an alpha level of 0.05, 20% loss to follow-up, and ICCs ranging from 0.03 to 0.05. Assuming we accrue an average of 50 survivors per practice (minimum sample of at least 600 survivors), we will have at least 80% power provided the rate of CVH discussions under the usual care condition is ≤15%, and that exposure to the AH-HA tool raises the rate of CVH discussions to 35% or more. If the rate of CVH discussions is higher in the usual care group (i.e. 20%), then the rate of receipt of CVH discussions will need to be 40% or more in the AH-HA group to have >80% power.

Table 4. Power for various total practices with an average of 70 participants by ICC and 20% difference in CVH discussion rate.

ICC	pUC	pAH-HA	Total Practices	Power
0.03	10%	30%	8	91.9
			10	96.4
			12	98.4
	15%	35%	8	87.0
			10	93.2
			12	96.6
	20%	40%	8	82.8
			10	90.2
			12	94.5
0.04	10%	30%	8	86.3
			10	92.7
			12	96.3
	15%	35%	8	80.2
			10	88.1
			12	93.1
	20%	40%	8	75.4
			10	84.1
			12	90.0
0.05	10%	30%	8	80.6
			10	88.4
			12	93.3
	15%	35%	8	73.7
			10	82.7
			12	88.8
	20%	40%	8	68.6
			10	78.0
			12	85.0

With a potential for fewer practices (i.e. 8-10) instead of the originally projected 12, increasing the average number of participants per practice to 70 will maintain adequate power for the same 20% difference (or more) shown in Table 3 scenarios. This still incorporates up to 20% loss to follow-up with ICCs ranging from 0.03 to 0.05 (Table 4). There are a few scenarios where we are slightly underpowered (shaded in grey in Table 4), but feel this is a necessary tradeoff between number of practices and survivors enrolled at overly conservative ICC values. We acknowledge that the overall sample size of survivors may change depending on the final number of practices recruited for the trial, but we anticipate the number of survivors enrolled to be between 560-700

total. And practices may recruit variable numbers of survivors, as long as we average 50 per practice for 12 total practices or average 70 per practice for 8-10 total practices, power will be maintained as shown in the tables above.

The planned subgroup analyses (receipt of cardiotoxic cancer treatment and having a primary care visit in the past year) will be largely exploratory. We will be well-powered to detect scenarios where the intervention's effect is isolated to a particular subgroup, for example, if the AH-HA tool increases CVH discussions only in individuals that had not seen a PCP in the past year, but is ineffective in individuals with such a visit. For example, based on simulation, conservatively assuming that 20% of participants will not have had a primary care visit in the past year (in OSU data, 79% of breast cancer survivors had a primary care provider documented in the EHR), power to detect such an interaction will be >80% provided the rate of CVH discussions is slightly more than doubled in those without a primary care provider. In subgroup analyses, we will additionally consider variation due to survivor characteristics such as sex and age.

The outcome of at least one visit to primary care providers/cardiologists in the prior year shares the same data structure (binary outcome observed at a single point in time) as our primary outcome; the power calculations presented in the previous section also apply. We focus our calculations on the ability to detect a difference at one-year for BMI, which showed improvements in our primary care pilot data from OSU. We expect that we will not show appreciable changes in smoking status, diet, and physical activity levels with use of the AH-HA tool. Assuming an ICC of 0.04, 50 participants per clinic (12 clinics), and a standard deviation of 5.8 kg/m^2, we will have >80% power to detect a 2.5 kg/m^2 mean difference in BMI between the intervention and usual-care groups.

10.5 Secondary Objectives, Endpoints, Analysis Plans

As outlined in section 7.3, we will also ask survivors about (1) having a primary care provider and cardiologist, (2) the number of visits, and (3) date of last visit to primary care providers and cardiologists in the past year, query the EHR for documentation, and obtain consent to obtain medical records to ascertain out-of-network visits. Secondary analyses will include survivor and provider covariates (e.g., survivor and provider age, survivor sex, cancer type), HRSA data (https://data.hrsa.gov/tools/shortage-area/hpsa-find) which will identify health professional shortage areas, and baseline CV risk to assess the effect of these factors on outcomes and to see if the intervention effect is more pronounced in certain subgroups. We will use a similar analytic framework (mixed effects logistic models) to assess the effect of the intervention on primary care and cardiology referrals/visits and the ordering of CVH-relevant laboratory tests or treatments during the one-year follow-up period. We hypothesize that the proportion of referrals will be higher in intervention compared to usual care clinics; we expect the proportion of referrals to increase from baseline to one-year in the intervention clinics but not usual care clinics (the effect of intervention fidelity: being exposed to the AH-HA tool).

Similar in the approach for the primary objective, a mixed effects logistic regression model will assess the effect of the intervention on the likelihood of at least one visit to primary care in the past year at one-year follow-up, controlling for whether the participant visited a primary care provider in the year prior to study baseline. We expect that the proportion of completed primary care visits will increase from baseline to one-year in the intervention clinics but not usual care clinics (the effect of intervention fidelity: being exposed to the AH-HA tool). We will similarly use linear mixed effects models to compare the change in CVH risk factors (BMI, cholesterol, blood pressure, etc.) between the study groups including baseline levels of these risk factors as a covariate in the mixed models. We will conduct sensitivity analyses using multiple imputation to examine the effect of missing follow-up data on inference for these analyses.

10.6 Analysis Plan for Key Informant Interviews

Key Informant Interview analyses will be descriptive in nature and will help determine strategies for future dissemination and implementation of the AH-HA tool. The results of this aim will also be used more generally to inform best practices for EHR-based tool implementation in community-based oncology clinics. Interview transcripts will be analyzed using ATLAS.ti software (Atlas.ti Scientific Software Development) and follow the principles and procedures of thematic analysis (TA). TA is a rigorous and widely-used approach that identifies, categorizes, and contextualizes patterns of key themes and explores behavior, interpretation, and consequences of experiences[114]. Thematic statements regarding barriers and acceptability of future AH-HA tool maintenance or implementation will be generated to summarize key ideas while also preserving the complexity of inter-related ideas. These statements will seek to integrate information regarding barriers and facilitators with information regarding practice and provider characteristics and the likelihood of future implementation. Drs. Weaver and Lee will oversee trained Q-PRO staff within the Q-PRO to produce a description of key themes and supporting quotes, a methodology previously implemented by Drs. Weaver and Foraker.[115]

10.7 Evaluation of Response

All participants with a completed baseline post-visit survivor survey will be included in final analysis for survivors. Key informant analyses will include all surveys and interviews conducted.

11. REGISTRATION PROCESS

11.1 Investigator and Research Associate Registration with CTEP

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam. In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr.

RCR utilizes five person registration types:

- IVR — MD, DO, or international equivalent;
- NPIVR — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- AP — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System [RUMS], OPEN, Rave, acting as a primary site contact, or with consenting privileges;
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents: Documentation Required	**IVR**	**NPIVR**	**AP**	**A**	**AB**
FDA Form 1572	✓	✓			
Financial Disclosure Form	✓	✓	✓		
NCI Biosketch (education, training, employment, license, and certification)	✓	✓	✓		
GCP training	✓	✓	✓		
Agent Shipment Form (if applicable)	✓				
CV (optional)	✓	✓	✓		

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster;
- Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN;
- Act as the site-protocol Principal Investigator (PI) on the IRB approval; and
- Assign the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

In addition, all investigators acting as the Site-Protocol PI (investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, or as the CI on the DTL must be rostered at the enrolling site with a participating organization. Additional information is located on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the **RCR Help Desk** by email at RCRHelpDesk@nih.gov.

Protocol documents are found on the CTSU website, but supplemental documents may be available on the Wake Forest NCORP Research Base website.

11.2 Cancer Trials Support Unit Registration Procedures

Protocol documents are found on the CTSU website, but additional supplemental documents may be available on the Wake Forest NCORP Research Base website (https://wakencorp.phs.wakehealth.edu/dspLogin.cfm).

This study is supported by the NCI CTSU.

IRB Approval

For CTEP and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB). In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific

regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet (SSW) for Local Context to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by emailing the email address above or calling 1-888-651-CTSU (2878).

In addition, the site-protocol Principal Investigator (PI) (i.e. the investigator on the IRB/REB approval) must meet the following criteria in order for the processing of the IRB/REB approval record to be completed:

- Holds an active CTEP status;
- Active status at the site(s) on the IRB/REB approval on at least one participating organization's roster;
- If using NCI CIRB, active on the NCI CIRB roster under the applicable CIRB Signatory Institution's record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile;
- Lists all sites on the IRB/REB approval as Practice Sites in the Form FDA 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements

Additional site requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO);
- An active roster affiliation with the NCI CIRB roster under at least one CIRB Signatory Institution (US sites only); and
- Compliance with all protocol-specific requirements (PSRs).

Protocol Specific Requirements For WF-1804CD Site Registration:

- NCI CIRB approval of the Site Submission Worksheet – all participating sites must use the NCI CIRB as their IRB of record for WF-1804CD.
- Site Open to Enrollment (SOTE) letter from WF NCORP RB, which is provided to the site once sites have completed all site set up activities.

Practice Level Data Collection Form – The enrolling affiliate/subaffiliate will complete the NCORP Practice Level Data Collection Form and submit it to the CTSU Regulatory Office as a *Specific Sites only* submission using the Regulatory Submission Portal located in the Regulatory section of the CTSU website. The form will collect various attributes about the enrolling affiliate/subaffiliate. All of the questions on the form must be complete and the distribution for the analytic cases question must equal 100%. (See form for directions). The form must be received and complete for site registration approval in RSS. The NCORP Practice Level Data Collection Form requirement is submitted once for participation on all NCORP Cancer

Care Delivery (CCDR) trials, but will expire two years after it is received. NCORP sites will need to resubmit the Practice Level Data Form to the CTSU in order to continue to enroll to CCDR trials.

Upon site registration approval in RSS, the enrolling site may access OPEN to complete enrollments. The enrolling site will select their credentialed provider treating the subject in the OPEN credentialing screen, and may need to answer additional questions related to treatment in the eligibility checklist.

Submitting Regulatory Documents:

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal on the CTSU members' website.

To access the Regulatory Submission Portal log in to the CTSU members' website, go to the *Regulatory* section and select *Regulatory Submission*.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org in order to receive further instruction and support.

Checking Site's Registration Status:

Site's registration status may be verified on the CTSU members' website.

- Click on *Regulatory* at the top of the screen;
- Click on *Site Registration;* and
- Enter the sites 5-character CTEP Institution Code and click on Go.
    - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with NCI or their affiliated networks.

11.3 Patient Enrollment

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the LPOs registration/randomization systems or the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the enrollment data in WF NCORP RB's clinical data management system, REDCap.

Requirements for OPEN access:

- A valid CTEP-IAM account;

- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or participating organization PO roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus registration type;
- If a Delegation of Tasks Log (DTL) is required for the study, the registrar(s) must hold the OPEN Registrar task on the DTL for the site; and
- Have an approved site registration for the protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR. If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

Prior to accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes; and
- All patients have signed an appropriate consent form and Health Insurance Portability and Accountability Act (HIPAA) authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. You may print this confirmation for your records.

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at https://www.ctsu.org or https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

Non-patient Provider and/or Other Professional Discipline enrollments, for this trial will be completed using OPEN. All OPEN access requirements apply to non-patient enrollments in OPEN.

Prior to enrollment, site staff should verify the following:

- Non-patient participant has met all eligibility criteria within the protocol stated timeframes; and
- All non-patient participants have signed an appropriate consent form and HIPAA authorization form (if applicable)

In the OPEN credentialing screen, select the registration type of non-patient and select the applicable non-patient type Provider and/or Other Professional Discipline. Complete the non-patient enrollment prerequisite questions and the associated eligibility checklist and submit the enrollment. The OPEN system will provide the site with a printable confirmation of the non-patient registration and additional instructions as needed. Please print this confirmation for your records.

11.4 Data Submission / Data Reporting

REDCap is a clinical data management system being used for data collection for this trial/study. Access to the trial in REDCap is granted through Wake Forest NCORP Research Base.

Requirements to access REDCap:

- A valid CTEP-IAM account; and
- Must have a minimum of an Associate Plus (AP) registration type;
- Must be on the Wake Forest NCORP Research Base roster in NCORP-SYS for active study sites

Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.

Upon initial site registration approval for the study in Regulatory Support System (RSS), all persons on the Study Site Role form from the Study Start-up Packet needing database access will be sent a study invitation e-mail from REDCap with instructions for access. Please note, site users will not be able to access the study in REDCap until all required study specific trainings are completed.

For any additional questions on REDCap contact the Wake Forest NCORP Research Base at 336-716-0891 or NCORP@wakehealth.edu.

11.5 Informed Consent

All potential survivor participants will be consented with a ***Survivor Consent Script*** whether they are consented virtually, by telephone, or in-person. The study has requested a waiver of documentation of consent for survivor participants. Provider key informants will give their consent by reading the provider key informant consent in REDCap and proceeding to the ***Post-Training Provider Structured Survey*** questions. Administrator/IT specialist key informants will give their consent by reading the administrator/IT specialist consent and proceeding to the ***Eligibility, Demographic & Background*** questions. Participants will be given a copy of the IRB-approved Informed Consent information to review, if requested. The investigator or other designated study staff will explain all aspects of the study in lay language and answer all questions regarding the study. Subjects who refuse to participate or who withdraw from the study will be treated without prejudice.

Prior to study initiation, the informed consent document must be reviewed and approved by NCI, DCP and/or DCCPS, the Wake Forest NCORP Research Base, and the NCI CIRB. Each Organization at which the protocol will be implemented will also need to get approval from the NCI CIRB to participate in the study. Any subsequent changes to the informed consent must be approved by NCI, DCP, Wake Forest NCORP Research Base and the NCI CIRB. All approved changes are then implemented by each local organization in the required time period and if required locally, submitted to each organization's local IRB for approval prior to initiation.

11.6 Other

This trial will be conducted in compliance with the protocol, Good Clinical Practice (GCP), and the applicable regulatory requirements.

APPENDIX A: VIRTUAL VISIT CONSIDERATIONS

For both usual care and intervention sites, the designated AH-HA appointment may be conducted virtually only if the survivorship care visit is already scheduled as a virtual visit; otherwise, the designated AH-HA appointment should be conducted in-person.

For intervention sites only, the provider and participant must be able to videoconference with screen sharing that shows the participant the AH-HA tool.

Considerations for virtual visits are listed below:

Recruitment and Consenting

- Eligibility: Because surveys can only be completed online via REDCap in English, Spanish speakers/readers will be able to participate in the study only if study sites can meet the following requirements:
    - Mail paper copies of the surveys in Spanish prior to the designated AH-HA appointment so that the survivor can complete and return the ***Pre-visit Baseline Survivor Survey*** within the two week window prior the designated AH-HA appointment.
    - Have a Spanish-speaking provider conduct the designated AH-HA appointment or include an interpreter in the virtual visit videoconference.
    - Conduct the ***Post-visit Baseline Survivor Survey*** by phone with a Spanish-speaking staff member or interpreter within 48 hours of the designated AH-HA appointment or mail paper copies of the surveys in Spanish prior to the appointment so that the survivor can complete the ***Post-visit Baseline Survivor Survey*** immediately after the appointment.
- Screening: Local NCORP site staff should screen schedules for survivorship care virtual visits to identify participants who would need to be contacted virtually for study invitation and consenting.
- Email Collection:
    - Survivor emails will be collected during recruitment and added to the Site Info Entry form in REDCap in order for the surveys to be emailed to the participant.
    - Provider key informant emails need to be collected during recruitment and entered into the Site Info Entry form in order to receive the diet and exercise status answers that the participant provides (see ***Diet and Exercise Status*** under the Designated AH-HA Appointment section below).
- Consenting: The study has requested a waiver of documentation of consent for all participants. The ***Survivor Consent Script*** provides a telephone/teleconference script for virtual or telephone consent.

Designated AH-HA Appointment

- AH-HA Patient Notification: The ***AH-HA Patient Notification*** form is intended to remind the provider to use the AH-HA tool with the patient during an in-person designated AH-HA appointment. However, for virtual visits, this physical reminder is not possible, so sites should flag that the patient is an AH-HA study participant somewhere in the EHR and/or scheduling module.

- Vitals Collection: Sites can ask in their virtual visit reminders for the survivor to provide as many AH-HA specific vitals as possible that they can conduct safely at home (weight and blood pressure). In the absence of day-of vitals, the AH-HA tool will pull the most recent data stored in the EHR.

- Diet and Exercise Status: For virtual visits, answers to the two diet and exercise questions will be automatically pulled from the ***Pre-visit Baseline Survivor Survey*** into a separate REDCap form and emailed to the provider.

- Medical Record Abstraction: Local site staff should record the format of the designated AH-HA appointment (in-person or virtually via telephone or video) and the reason why on the ***Medical Record Data Form*** in REDCap. This will be completed after the survivor completes the ***Post-visit Baseline Survivor Survey***.

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