SWOG’s NCI Community Oncology Program (NCORP) Research Base Concept/Capsule Submission Process

An Investigator’s Guide on How to Prepare and Submit a Concept/Capsule through SWOG’s NCORP Research Base
 *This information does not apply to concepts/capsules that start and develop in SWOG’s National Clinical Trials Network (NCTN).*

 **

**Table of Contents

The Must-Know Basics**

1. [The Difference between NCTN and NCORP Trials](#ref1_Trials)
2. [Definition of a Concept/Capsule](#ref2_Concept)
3. [Definition of a Protocol](#ref3_Protocol)
4. [The Six Major Milestones](#ref4_Committees)
5. [Concept, Funding, and Feasibility Plans’ Development Stages](#ref5_Stages)
6. [Roles and Responsibilities](#ref6_Roles)

**The Review and Submission Process**

* + - 1. [Investigator has a Study Idea and Shares the Idea with the Appropriate Committee
			Co-Chairs](#ref7_MonthlyMtg)
			2. [Investigator Drafts 1-Page Write Up](#ref8_OnePage)
			3. [NCORP Executive Committee Review 1-Page Write Up](#ref9_NCORPExRev)
			4. [Investigator Collaborates with the Research Community to Develop an Approved Study Idea](#ref10_ConceptDev)
			5. [Developing a Funding Plan](#ref11_FundingPlan)
			6. [Developing a Feasibility Plan](#ref11_FeasibilityPlan)
			7. [Co-Chairs Sign off on Fully Developed Concept](#ref12_SignOff)/Capsule
			8. [Statistical Review](#ref13_StatsRev)
			9. [Preparing Slides for Triage](#ref14_Slides)
			10. [Triage Review Call](#ref15_Triage)
			11. [Financial and Feasibility Call](#ref16_FFCall)
			12. [NCI’s Division of Cancer Prevention Reviews Concept](#ref17_NCIDCP)
			13. [Begin Writing the Protocol](#ref26_Protocol)

**Available Funding Sources within SWOG**

1. [Investigator Applies for NIH Grant and Lists SWOG as a Subcontractor](#ref18_NIHSub)
2. [Clinical Trials Initiative (CTR) Contracts](#ref19_CTR)
3. [Nationwide: Services and Storage for Biospecimens](#ref20_Nationwide)
4. [SWOG Trial Support (STrS)](#ref20_STrS)
5. [Division of Cancer Prevention (DCP) Funds](#ref22_DCPFunds)
6. [Biomarker, Imaging, and Quality of Life Studies Funding Program (BIQSFP)](#ref23_BIQSFP)
7. [The Hope Foundation](#ref24_THF)

**Appendix**

1. [SWOG NCORP Contact List](#ref29_ContactList)
2. [SWOG Concept/Capsule Summary Form](#ref25_SWOGform)
3. [Example: 1-Page Study Idea](#ref27_1pageEX)
4. [Example: 10-Page Fully Developed Concept/Capsule](#ref28_10pageEX)

**[The Difference between NCTN and NCORP Trials](#ref0_TOC)**

|  |  |  |
| --- | --- | --- |
|  | **National Cancer Trial Network Trials (NCTN)** | **NCI Community Oncology Research Program (NCORP) Trials** |
| **Themes** | * Focuses on the treatment and its impact on the disease.
 | * Focuses on the disease and its overall impact on the patient.
 |
| **Outcomes** | *Outcomes directly relate to survival:** Tumor response
* Survival outcomes
 | *Outcomes represent a broader assessment of the disease’s and treatment’s impact:** Patient reported outcomes
* Disease incidence
* Incidence of adverse events and treatment side effects
* Treatment utilization
* Financial outcomes
* Implementation and surveillance
 |
| **Study Objectives**  | * Clinical results from treatment trials
 | * Prevention and Epidemiology
* Symptom Control and Quality of Life
* Survivorship
* Cancer Care Delivery Research
 |
| **Intervention Types** | * Systemic therapies
* Surgery
* Radiation therapy
 | * Technological interventions
* Supplements and alternative medicines
* Organizational and physician interventions
* Behavioral and educational interventions
 |
| **Design Types** | * Single arm and randomized phase II trials
* Early therapeutics trial (phase I)
* Randomized phase III trials
* Patient level data on registered patients
 | * Cohort studies
* Randomized phase II-III trials
* Novel hybrid designs
* Multi-level designs
* Patient level data on registered patients
* Aggregate data on non-registered patients
* Physician and clinic level data
 |

**[Definition of a Concept/Capsule](#ref0_TOC)**

In SWOG, a concept/capsule **begins as a study idea, and then gradually develops** throughout the process.

Subsequently, **the concept/capsule fully develops** into a well-defined research question, consisting of a feasible plan that explains how the question will be answered (methodology), and what will be measured in order to answer the question (outcome).

 ![C:\Users\cwl2129\AppData\Local\Microsoft\Windows\Temporary Internet Files\Content.IE5\OZA1W6S4\lightbulb[1].gif]() ![C:\Users\cwl2129\AppData\Local\Microsoft\Windows\Temporary Internet Files\Content.IE5\SSM7GHQF\feuille%20mobile[1].png]()

 **Study Idea Fully Developed Concept
 1-page write up x ≤ 10 pages**

 **Concept=Capsule**

The light bulb represents a concept/capsule starting off as an idea. The notebook paper represents the full development of the idea.

**Important Tips:**

* Please see the appendix for an example of how a concept/capsule starts off as a study idea (1-page write up), then fully develops into a 10-page write up.
* The fully developed concept/capsule corresponds to SWOG Concept/Capsule Summary From, Section II. This section also contains instructions and guidelines on how to write a concept/capsule. Please see the appendix for the SWOG Concept/Capsule Summary Form.

**[Definition of a Protocol](#ref0_TOC)
A protocol** **is a document that describes step-by-step how to execute a clinical trial.**

The protocol describes the study objectives, background, eligibility, intervention, calendar, endpoints, statistical design, and the required forms for a study. It also describes in detail the materials, tools, and steps needed to screen and consent patients, collect data, and how to respond to certain kinds of situations.

The protocol is developed after NCI’s Division of Cancer Prevention (DCP) has approved a concept/capsule.

The investigator is typically given **90 days** from DCP’s concept/capsule approval date to complete and submit the first full version of the protocol.

*\*The graph below represents the six major milestones a concept/capsule needs to undergo before an investigator can begin writing a protocol.*

NCI’s DCP approves concept.

**[The Six Major Milestones](#ref0_TOC)**This following figure represents the six major milestones a concept/capsule will undergo in the development process. The concept/capsule will be reviewed in the order below. Generally, there will be a lot of back-and-forth communication among the investigator(s), co-chairs, statisticians, protocol coordinator, financial and budget staff, and patient advocate when developing, revising, and re-submitting a concept/capsule in between the six stages.

 *\*The first five review groups are SWOG-supported activities.*

Investigator gradually develops an approved idea and comes up with a funding and feasibility plan.

Investigator drafts study idea as a 1-page write up.

**[Concept, Funding, and Feasibility Plans Development Stages](#ref0_TOC)**

|  |  |  |  |
| --- | --- | --- | --- |
| **By this submission and review point…**  | **Concept Development Stage** | **Funding Plan Development Stage** | **Feasibility Plan Development Stage** |
| Research Committee’s Meetings | Study idea  | Identify, apply, and understand the best funding mechanisms.**Include** **Casey Dawson** **from Group Chair’s Office early and often if there are any budget-related conversations.**  | Identify, assess, and anticipate logistical-related issues that can hinder the study’s success. **Issues are not expected to be resolved.** |
| NCORP Executive Committee | Study idea  |
| Statistical Review | Fully developed concept/capsule | Same as above. | Same as above.  |
| Triage Review | Fully developed concept/capsuleA separate translational medicine proposal will also need to be submitted, if there is a translational medicine component.  | Same as above.If an investigator is in the process of applying for external funding, an approval by the Triage Review can lead to a letter of support from the Group Chair’s Office. | Same as above. |
| Financial and Feasibility Call  | Fully developed concept/capsule | Lay questions and issues on the table so the study team and Group Chair’s and Operation’s Offices can resolve together.Determine different sources of funding, including industry funds, external grants, etc. | Lay questions and issues on the table so the study team and Group Chair’s and Operation’s Offices can resolve together.  |
| NCI’s Division of Cancer Prevention | Fully developed concept/capsule | All issues should be resolved.  | All issues should be resolved. |

**[Roles and Responsibilities](#ref0_TOC)**

**Investigator – Study Idea’s Primary Advocate and Developer**The investigator proposes a study idea and is the primary force in developing the study idea into a scientific research plan, coming up with a funding and feasibility plan, and applying for financial support for his/her study. The investigator also answers and responds to questions regarding the medical, scientific, and budgetary issues that come up during the development phase. (Alternatively, an investigator is also known as the study chair.)

 **Co-Chairs – Help Investigator Figure Out How to Make the Trains Run**The committee’s co-chairs’ primary responsibility is to mentor an investigator by giving advice, feedback, and reactions to the investigator’s idea and its subsequent development. The co-chairs point the investigator in the right direction, giving the correct signals and tactics to move in the right way. As a result, the investigator can continue developing his/her study idea, re-direct his/her energy elsewhere, or stop investing his/her time and effort into a study idea that ultimately will not be successful.

**Executive Officers – Understand, Assess, and Provide Insights to the General Lay of the Land**
Executive officers (EOs) focus on the bigger, higher level picture: they use their unique insights and broad scientific expertise to give co-chairs a general direction. Executive officers also assess the research committees’ whole portfolio in relation to SWOG’s priorities and provide suggestions on how to improve the concept development and approval process. They also participate on committee calls, NCORP Executive Committee Call, and the Triage Review Call, giving feedback and a reality check in order to determine what is feasible within SWOG. In addition, they serve as mentors in the Young Investigator Training Course and during the protocol development for their assigned committees.

**Primary Statistician** **– Helps Investigator** **Design a Plan that Turns a Research Question into an Executable Study**

The primary statistician is heavily involved in designing the overall study. The primary statistician works closely with the investigator to define the research question and ensures the study design will operate as a feasible experiment that will answer the question. The primary statistician also ensures that the overall study design and its statistical foundation will generate valid data. In the end, a strong statistical design will help the investigator get an answer that will be highly believable, trustworthy, and convincing.

**Secondary Statistician – Helps Develop the Protocol and Ensures the Protocol Achieves Consistent Data Collection**The secondary statistician is a master’s level statistician who is especially involved after a concept/capsule has been approved by NCI’s DCP. The secondary statistician helps create the protocol by developing the case report forms, designing the data bases, and guiding the protocol review process. Ultimately, the secondary statistician needs to ensure the protocol achieves consistent data collection because the statisticians will be analyzing the data in the end.  **Protocol Coordinator – Helps Move Things Along and Serves as a Resource and Distributor of Information**In the concept/capsule development process, the protocol coordinator assists an investigator by sending information, answering questions, and providing clarification regarding the concept development process and procedures. The protocol coordinator also assists co-chairs with prioritizing concepts and making connections within SWOG across different groups or entities.The protocol coordinator ensures concepts/capsules have been reviewed by all relevant parties and have been properly formatted. The protocol coordinator submits the final concept to NCI and distributes information about the concept/capsule to the appropriate individuals.

**Patient Advocate – Provides the Perspective of a Cancer Patient and Potential Clinical Trial Participant**The patient advocate provides the perspective of what it’s like for the patient and his/her family to live with the disease. The patient advocate experiences things in real life that researchers do not know but should take into consideration. In addition, the patient advocate reviews the concept to assess potential obstacles for patient accrual and the study’s desirability.

**Data Coordinator – Manages and Performs Quality Control on Data**

The data coordinator provides input during the study development and performs a quality review of data after a study has been activated. The data coordinator also acts as a liaison and reference point to study sites regarding protocol eligibility, data completion, and submission questions. During the protocol development process, the data coordinator provides input from a data management perspective on the protocol and case report forms.

**Statistics and Data Management Center (SDMC)**The SDMC provides expertise in the design, implementation, data collection and review, monitoring, analysis and interpretation of SWOG trials and translational medicine studies.  The statisticians and data coordinators are located at the SDMC in Seattle, Washington.

**Group Chair’s and Operation’s Offices – Equivalent to SWOG’s Headquarters**
The Group Chair’s Office is responsible for leading SWOG's vision and direction, overseeing its operations, negotiating contracts with third parties, delivering its communications appropriately, and ensuring the tax dollars that fund research are spent wisely and tracked properly. The Group Chair’s Office also makes sure those dollars keep coming in. The Group Chair’s Office is located in Portland, Oregon.

The Operation’s Office oversees auditing, protocol development, group meeting management, membership and site enrollment, adverse event reporting, etc. The Operation’s Office is located in San Antonio, Texas.

Even though the Group Chair’s and Operation’s Offices are located in two separate locations, they function as one unit. The two offices are not separate and independent.

**Key SWOG Staff from the Chair’s and Operation’s Offices**
Chief of Administration – Nathan Eriksen
Budget and Financial Management Staff – Casey Dawson, Pat Mize, Tameka Lewis
Legal Staff – Edie Van Putten, J.D., Tristan Parker, J.D. (contracts attorneys)
Operations – Dana Sparks, Gretchen Goetz

**[Investigator has a Study Idea and Shares the Idea with the Appropriate Committee Co-Chairs](#ref0_TOC)**

1. Investigator has a study idea that h/she would be interested in pursuing.
2. Investigator shares his/her study idea with co-chairs and protocol coordinators in informal settings (i.e. SWOG group meetings, e-mail exchanges, etc.).
3. Co-chairs invite investigator to present his/her study idea at its committee meetings.
Committee meetings are designated for investigators to present their ideas, provide study updates, and address issues and challenges.
4. Investigator presents his/her idea during the committee meeting.

Ideally, the investigator also gets introduced to the committee’s primary statistician and patient advocate; however, no statistical design input should be contributed at this point.

1. Co-chairs and committee members have the opportunity to ask questions and provide feedback and advice to the investigator.
2. Co-chairs ask if there is support and enthusiasm for the investigator to draft a 1-page write up.

 7. Investigator drafts 1-page write up.

**[Investigator Drafts 1-Page Write Up](#ref0_TOC)**

The 1-page write up will be used by the NCORP Executive Committee to help determine the study idea’s feasibility and priority within SWOG, and to allocate SWOG’s resources accordingly.

1. Investigator drafts the 1-page write up. **Detailed statistics are not required.**
2. There is no formal format, but the write up should include the following four elements:
* Background
* Study population
* Primary outcome
* Study design (i.e. randomized two-arm trial, single arm pilot study, etc.)
1. Investigator submits his/her 1-page write up to the co-chairs.
2. Co-chairs submit 1-page write up to the NCORP Executive Committee.
3. 1-page write up will be reviewed by the NCORP Executive Committee.

**Timeline**

The NCORP Executive Committee has its call every fourth Wednesday of the month at 12 p.m. EST/11 a.m. CST/9 a.m. PST. Co-chairs should submit all 1-page write ups by Sunday evening before the review call on Wednesday. Investigator is not on the call.

**Important Tip:**
Please see the appendix for an example of a study idea as a 1-page write up.

**[NCORP Executive Committee Discusses 1-Page Write Up and Evaluates if the Study Idea is a High Priority and Feasible within SWOG](#ref0_TOC)**

1. Assistant to the NCORP Research Base’s Vice Chair helps prepare the NCORP Executive Committee Call. The assistant asks the co-chairs to submit any new 1-page write ups and distributes the write ups to the Committee members.

Listed below are participants who make up the NCORP Executive Committee:

**NCORP Research Base’s Vice Chair:** Dawn Hershman

**Executive Officers:** Gary Lyman, Katherine Crew

**Senior Advisor:** Frank Meyskens **Statistical Center:** Joe Unger, Katherine Guthrie, Monica Yee (program manager)

**Operation’s Office:**  Gretchen Goetz, Patricia O’Kane, Nicki Treviño, Sandi Hita

1. NCORP Executive Committee reviews write ups for feasibility, issues and challenges, clinical impact, research priorities, etc.
2. Feedback is given to investigator within 24-48 hours.
3. Investigator continues to develop and to revise the study idea. If additional issues need to be addressed before the study idea can move forward, the investigator is welcomed to re-submit his/her study idea to the NCORP Executive Committee.
4. When the NCORP Executive Committee has decided to move forward with a study idea, the Committee assigns which research committee is best suited to house the study idea. Assigning the study idea to the most appropriate research committee determines the subsequent resource allocation.

In certain circumstances, the co-chairs need to approve housing a study idea to ensure there are enough resources available in their committee.

1. **When a study idea has been approved to go forward, a statistician from the SWOG’s Statistical Center will become involved in developing the study idea.**In order to conserve resources, statisticians from SWOG’s Statistical Center will not be involved until a study idea has been approved to go forward.

**[Investigator Collaborates with the Research Community to Develop an Approved Study Idea](#ref0_TOC)**

1. Before the investigator begins developing an NCORP Executive-approved study idea, h/she should know the following:
* Assigned research committee and its corresponding co-chairs, protocol coordinator, primary statistician, and patient advocate. **This is your study team.****Please see the appendix for the SWOG NCORP Contact List to see each research committee’s co-chairs, primary statistician, protocol coordinator, and patient advocate.**
* Complete the Investigator’s Study Chair Workshop **or** Young Investigator Training Course (YITC)
* The Study Chair Workshop is an online course that can be taken at any time by an investigator. The training course can be found under the “Training” section when an investigator has logged onto SWOG’s website. Contact SWOG training manager for assistance.
* The YITC course is an annual workshop that young investigators can apply for and be selected to participate in person, in Seattle, WA. <http://thehopefoundation.org/research-funding/juried-programs/young-investigator-training-course-yitc/>
1. What the investigator should be simultaneously preparing for at this stage:
* **Developing a** **funding plan**: planning what needs to be budgeted, understanding the most appropriate funding mechanisms and their related instructions and timelines, and applying for funding opportunities.
* **Developing a feasibility plan**: thinking about what a study needs (i.e. staff, supplies, vendors, labs, drug distribution costs, shipping costs, equipment, surveys, etc.) and how those needs will be paid, delivered, and managed in a timely manner.
1. Investigator collaborates with other colleagues, executive officers, co-chairs, primary statistician, and patient advocate to fully develop a concept/capsule.
**Please see the appendix for an example of a fully developed concept/capsule as a 10-page write up.**
2. **How to Develop and Write a Successful Concept: Guidelines from NCI’s DCP**Please see **SWOG Concept/Capsule Summary Form, Section II** for guidelines and instructions. These instructions and guidelines are from NCI’s DCP and will be used by both Triage and NCI’s DCP when reviewing a concept/capsule. **Please see the appendix or ask the protocol coordinator for the SWOG Concept/Capsule Summary template.**

**Important Tips:**

* **Engage and involve the patient advocate early and often** in the concept/capsule development process. The patient advocate wants to establish a good working relationship with the investigator instead of getting involved at the last minute when the protocol coordinator asks the patient advocate to review the concept and to complete a Power Point slide right before the Triage Review Call. More importantly, a patient advocate will provide the insights of the financial burden when participating in studies (i.e. who will pay for the study’s costs that are not covered by the insurance companies?)
* **Be the driver:** It is very important for the investigator to take ownership and to drive the process forward. Driving the process forward means consistently following up with all relevant parties and making sure your concept is moving forward. Unnecessary delays are caused by everyone waiting for something else, or thinking someone is doing something when that is not the case. **Do not be bashful to follow up or to ask for support.**
* If there is a translational medicine component, a separate proposal will also need to be submitted. Please ask the protocol coordinator for this document.
* Engage the translational medicine committee and consider translational medicine secondary endpoints, if appropriate.

**[Developing a Funding Plan](#ref0_TOC)**

|  |  |
| --- | --- |
| **External FundingInvestigator brings in outside funding** | **Internal FundingInvestigator utilizes the available funding sources within SWOG** |
| * Peer-reviewed grants from NCI (i.e. R01, R03)
* Institutional grants
* Insurance company’s reimbursement for standard of care procedures
* Support from industry
 | * Investigator applies for a NIH grant and lists SWOG as a subcontractor
* Clinical Trials Initiative Contracts
* Nationwide Laboratory
* SWOG Trial Support (STrS)
* DCP Funds
* Biomarker, Imaging, and Quality of Life Studies Funding Program (BIQSFP)
* The Hope Foundation
 |

Investigator has two possible routes when determining the funding sources and coming up with the funding plan:

 **SWOG’s federal grants from the NCI do not pay for every aspect of a study.** Please see “Available Funding Sources within SWOG” for more details when considering using the above internal funding sources.

**In general, SWOG’s federal grants support SWOG’s infrastructure, which include the following:**

* Staff at the Statistical Center, Group Chair’s and Operation’s Offices
* Legal staff to help negotiate contracts with pharmaceutical companies
* Auditors to perform quality assurance and to audit sites
* Organization of bi-annual Group meetings
* Payment to sites to accrue patients, submit data, and fulfill regulatory requirements
* Payments to sites to develop, activate, and manage a study

**In general, the following items require outside funding:**

* Drug supply and distribution
* Correlative studies
* Study coordinator support for burdensome PRO collection or intervention
* Sample collection and storage
* Non-standard of care costs
* Extra patient-reported outcomes (PROs)
* Salary support and travel for investigators

**Important Tips:**

* Co-chairs will usethe specific aims, study schema, and intervention to quickly assess how big the study will be, the appropriate funding mechanism(s), and if the study will need any special funding.
* Pay attention to incorporating insurance company reimbursements’ limitations and schedules into study design. Realize that the insurance benefit designs and policies vary not only by insurance carrier (i.e. United Healthcare, Aetna, Cigna, etc.) but also by lines of business (i.e. traditional Medicare, managed Medicare, Medicaid, employer-based fully insured, individual market).
* Discuss with the statistician about extensive data collection elements.
* **Include** **Casey Dawson** **from Group Chair’s Office early and often if there are any budget-related conversations. Investigators need to observe what is and is not allowed within SWOG while forming a partnership with a third party (i.e. pharmaceutical company). The Group Chair’s Office will help investigators navigate this process.**

**Helpful Planning Guides:**

* **Please see SWOG Capsule Summary Form, Section III – Resource Plan** to help start thinking about what needs to be budgeted. The investigator should know how to answer Section III – Resource Plan by the time his/her concept is about to be submitted to Statistical Review.
* **Areas that might need extra funding:** An Excel document called “Budget Information Worksheet” will be used in the Financial and Feasibility Call to help the study team and Group Chair’s and Operation’s Offices highlight areas that might need extra funding. The Excel document does not need to be completed by the time of the Financial and Feasibility Call, but it will help the investigator become aware of areas that might need extra funding early in the process. Please ask the protocol coordinator for this document.

**Helpful Questions When Thinking about the Funding Plan:**

* What do I need to budget for?
* Where is the money coming from?
* What is and is not covered by SWOG’s grants?

[**Developing a Feasibility Plan**](#ref0_TOC)A feasibility plan explains a study’s needs (i.e. staff, supplies, vendors, labs, drugs, equipment, shipping costs, surveys, procedures, etc.) and how those needs will be paid, delivered, and managed in a timely manner. Below are some suggested guidelines on how to identify, anticipate, and organize a study’s needs.

1. Understand the underlying infrastructure, work flow, and processes behind the study. Be as precise as possible with the work flow’s steps in order to map out and anticipate a study’s needs. For example, in preparation for a serum-based biomarker study:

|  |  |  |  |
| --- | --- | --- | --- |
| **Work Flow’s Steps** | **Who will be providing my study’s needs?** | **What does my study need?**  | **What should I budget for?** |
| 1. Sites draw and process blood samples.
 | Site | Blood draws, freezer-friendly tubes (cryovials), tube racks | Supplies, technical cost to draw the blood, cost to cover blood draw that is not part of standard of care. |
| 1. Sites send processed blood to biobank for storage.
 | Site | Dry ice, shipping boxes | Mailing supplies, shipping cost from site to biobank. |
| 1. Biobank stores processed blood into -80◦ C freezer.
 | Biobank | N/A | Cost to store blood samples at biobank. |
| 1. Biobank sends frozen blood samples to local lab for biomarker analyses.
 | Biobank | N/A | Cost to prepare blood samples for shipping. Shipping cost from biobank to local lab. |
| 1. Local lab runs biomarker analyses.
 | Local lab | N/A | Cost to run the biomarker analyses, cost to run any special assays |

1. Risk assessment: What is the possibility of X, Y, Z happening that will impact the study’s underlying infrastructure?
* What happens to the study if the drug company pulls out?
* What happens if the outcomes from a pilot study are different from what I had anticipated?
1. Other things to consider that will be discussed on the Financial and Feasibility call:
* Issues raised during risk assessment
* Issues raised by DCP
* Accessibility of patients
* Participation: SWOG only? NCORP and NCTN? Non-U.S. sites?
* Collaborations with NCTN and Non-NCTN groups

**[Co-Chairs Sign off on Fully Developed Concept/Capsule](#ref0_TOC)
*This is a very important step!*** *Investigator should also have a very solid funding plan by this step when the concept/capsule is about to get submitted to the Statistical Review. Solid funding plan means, “A grant application is in progress, planning to submit a RO1, or applying for funds from this resource.”*

Co-chairs and investigator need to form a consensus that a concept/capsule has been fully developed before it can go to the Statistical Review.

1. Indicators of a fully developed concept/capsule:

* Does the concept/capsule have a well-defined, specific, and important question?
* Does the concept/capsule answer the question?
* Can the plan accrue patients? Are the plans feasible or are they too complicated?
* Are there any patient safety or any patient burden issues?
* Are there any major logistical and operational problems with the outcomes, study design, population, and sample size?
* **\*\*If the primary statistician still has questions about the study in order to do the statistical design, then it is not fully developed or ready to be submitted; however, the design should be done by this stage. \*\***
1. Protocol coordinator circulates the near-final draft of concept/capsule to co-chairs, statisticians, executive officer, and patient advocate for final review. Protocol coordinator fills out review dates in SWOG Concept/Capsule Summary Form – Section IV.
2. Protocol coordinator ensures all sections in the SWOG Concept/Capsule Summary Form have been completed. The statisticians review this form in its entirety. Sections that are blank indicate more thought is needed. A “quick answer” just to get something down is not sufficient. Each section should be thoughtfully addressed. If the investigator has questions or doesn’t understand, h/she should ask.
3. If the co-chairs feel the concept/capsule is ready for the Statistical Review, they will sign off on it. Both co-chairs need to sign off on the concept/capsule, but occasionally, one co-chair will sign off on the concept/capsule because h/she took a more prominent role in helping the investigator develop it.
4. **Protocol coordinator submits signed off concept/capsule and completed SWOG Concept/Capsule Summary Form to the assigned primary statistician**, who forwards the materials to the Statistical Center’s administrative staff to arrange the review.

**[Statistical Review](#ref0_TOC)**The primary purpose of the Statistical Review is for the study statisticians to get feedback from other SWOG statisticians and data coordinators on how to improve the design and other feasibility issues that may hinder the study. The Statistical Review also helps Mike LeBlanc and Cathy Tangen become informed about the study prior to Triage submission. Mike LeBlanc and Cathy Tangen represent the Statistical Center on the Triage Review Call.

1. What gets submitted to the Statistical Review:
* Completed SWOG Concept/Capsule Summary Form – All sections must be completed!
* Fully developed concept/capsule (corresponds to SWOG Concept/Capsule Summary Form’s Section II)
1. 10-15 statisticians and data coordinators from the Statistical Center review the SWOG Concept/Capsule Summary form in its entirety. This group forms the Protocol Review Committee, which reviews both concepts and protocols.
2. Statistical Center gives feedback and/or final comments to the investigator, co-chairs, and protocol coordinator.
3. Investigator incorporates feedback and comments into the concept/capsule.

**Timeline**

Statistical Review can happen any Wednesday if the concept/capsule is ready by the preceding Friday, except when there are too many other concepts or protocols already scheduled that week, or if too many statisticians are unavailable.

**[Preparing Slides for Triage](#ref0_TOC)**
Whenthe investigator has incorporated the final feedback from the Statistical Review, the next step is to prepare slides for the Triage Review Call.

1. Investigator asks the protocol coordinator for the Power Point slide deck. The slide deck also includes an individual slide for the patient advocate to complete.
2. Protocol coordinator sends the newly revised concept and individual slide to the patient advocate to complete.
3. Investigator and patient advocate submits the completed slides back to the protocol coordinator.

**Important Tip:**It’d be great to give the patient advocate more than one week to review the newly revised concept/capsule, so the patient advocate has time to digest the scientific material and to complete the slide.

**[Triage Review Call](#ref0_TOC)**The Triage Review Call is for the committee to evaluate if a concept/capsule is good science: does the concept fit with SWOG’s mission and priorities? Is the study worth doing? Is the scientific work meritorious? The committee also evaluates if the investigator has a good funding plan: does the investigator have a realistic sense of what needs to get funded, the best funding mechanism, and skills and experience needed to secure the funds?

1. What gets submitted to the Triage Review Call:
* Completed SWOG Concept/Capsule Summary Form – All sections must be completed!
* Fully developed concept (corresponds to SWOG Concept/Capsule Summary Form’s Section II)
* Power Point Slides
* SWOG Trial Support (STrS) Application Materials, if applicable

2. Investigator submits all materials to the protocol coordinator.

1. Protocol coordinator sends all submitted materials to Gretchen Goetz, who is the protocol operations manager, for placement on the Triage Review Call’s agenda.
2. Gretchen Goetz sends out the call-in information, date, and agenda to the investigator, co-chairs, patient advocate, and all relevant participants.
3. The Triage Review call is led by the SWOG Executive Committee. Listed below are participants who regularly attend all Triage Review Calls:

**SWOG Leadership:** Charles Blanke, Anne Schott, Dawn Hershman, Lee Ellis

**All Executive Officers:** Julie Gralow, Lisa Kachnic, Susan O'Brien, Chris Ryan, Craig Nichols, Manuel Valdivieso, James Rae, Gary Lyman, Katherine Crew

**Statistical Center:** Mike LeBlanc and Cathy Tangen

**Nationwide Bank:** Nilsa Ramirez and other representatives

**Patient Advocate:** Valerie Guild

**Pharmacy:** Siu-Fun Wong

**Group Chair’s Office:**  Nathan Eriksen, Casey Dawson, Pat Mize, Edie Van Putten, Tristan Parker, Wendy Lawton, Tameka Lewis

**Operation’s Office:**  Dana Sparks, Gretchen Goetz

The committee co-chairs and patient advocate are invited when a concept is being presented from their committee.

1. Triage Review Call’s Structure
* One hour web-based call
* Investigator and patient advocate presents their slides
* Q and A for investigator
* Co-chairs advocate for concept/capsule, explaining why the concept/capsule is important
* Q and A for co-chairs
* The Triage Panel privately discusses the concept, with the EO for that committee leading the discussion. The investigator is off the call, and a decision is made that day.
1. Four Possible Decision Outcomes:
* Approve as is
* Revise and no need to resubmit
* Revise and resubmit
* Disapprove
1. Panel notifies protocol coordinator about the decision and specific comments for official record-keeping. The protocol coordinator will distribute the information to the investigator, co-chairs, and to other individuals noted on the CC list of the review letter.
2. **When a concept/capsule has been Triage-approved, the Group Chair’s and Operation’s Offices will become involved in identifying, addressing, and resolving all funding and feasibility-related issues.**

**Timeline**
Triage Review Call occurs every Monday at 12 p.m. EST/11 a.m. CST/9 a.m. PST. Please submit the materials to the protocol coordinator by Tuesday in order to be reviewed in the proceeding weeks following submission.

**[Financial and Feasibility Call](#ref0_TOC)**The Financial and Feasibility Call is for the study team and Group Chair’s and Operation’s Offices to identify and to address the financial and pragmatic issues that will make a study a success.
SWOG is aware that NCI is on track of formalizing a timeline (Operational Efficiency Working Group) that dictates how soon a protocol needs to be completed, so a study can be activated in a timely manner. This timeline begins when a concept/capsule is submitted to NCI for review. (The timeline will re-set if a concept/capsule needs to be re-submitted.) It is important to resolve all financial and pragmatic-related issues before a concept/capsule gets submitted to NCI. Otherwise, delays that prevent timely study activation can prompt NCI to shut down the study.

In addition, the call kicks off the protocol development work and ensures everyone is on the same page.

1. There are no formal deliverables that need to be submitted for the Financial and Feasibility Call.
2. Protocol coordinator arranges the call with the following people invited:

**Study Team:** Executive Officer, Co-Chairs, Committee Vice-Chair, Investigator(s), Discipline Chair(s), Statisticians, Protocol Coordinator

**Group Chair’s Office:** Nathan Eriksen, Casey Dawson, Edie Van Putten, Tristan Parker, Pat Mize, Tameka Lewis

**Operation’s Office:** Dana Sparks, Gretchen Goetz

1. Call’s Structure:
* Introductions /roles and responsibilities of meeting participants
	+ OEWG clock – a protocol development timeline
	+ General study development process
* Feasibility of study plans – possible considerations:
	+ Issues raised during risk assessment
	+ Issues raised by DCP
	+ Accessibility of patients
	+ Participation: SWOG only? NCORP and NCTN? Non-U.S. sites?
	+ Collaborations with NCTN and Non-NCTN groups
* Funding
* Wrap Up and Review Action Items

**[NCI’s Division of Cancer Prevention Reviews Concept](#ref0_TOC)**

When all financial and feasibility issues have been resolved and address, the investigator informs the protocol coordinator when the concept is ready to be submitted to NCI’s Protocol Information Office (PIO).

1. What gets submitted to NCI’s PIO:
* Fully developed concept (corresponds to SWOG Concept/Capsule Summary Form – Section II)
* Cover Letter
* [Checklist](https://prevention.cancer.gov/clinical-trials/clinical-trials-management/protocol-information-office/pio-instructions-and-tools)
1. Protocol coordinator submits the concept/capsule and required forms directly to NCI via PIO. Many of the steering committees have time lines when a concept/capsule needs to be submitted to get on the next review. The protocol coordinator should be aware of these timelines.
2. **In situations where an investigator wants to simultaneously submit a federal grant (RO1, R21, etc.) AND a concept to NCI’s DCP:**
	1. A federal grant and a DCP concept cannot be submitted simultaneously for review. Two federal review bodies cannot review the same study.
	2. **Submit study’s aims to NCI’s DCP, so DCP is aware.** **Aims need to be submitted to DCP one month prior to submitting a grant to the funding agency; however, aims can be submitted before a concept goes to Triage. Dr. Hershman will submit the aims to DCP.**
	3. Hold off submitting a concept to DCP until you have received a score for your grant.
	4. If grant is funded, then submit a protocol to DCP.
	5. If grant is ultimately not funded, revise based on reviews/recommendations, and then submit to DCP as a concept.
3. If an investigator wants to submit a concept to DCP, the concept/capsule will be reviewed by one of the following steering committees at NCI:
* Cancer Care Research Delivery Steering Committee
* Prevention Steering Committee
* Symptom Management and Health-Related Quality of Life Steering Committee
* Other NCI Review
1. Steering committee call is scheduled.
Some committees will invite the investigators to interact via teleconference to answer a few questions at the beginning of their review.
2. Three Possible Decision Outcomes:
* Approve as is
* Pending/Needs revisions
* Disapprove
1. When a concept/capsule is approved by NCI, the study team can begin writing the protocol.

**[Begin Writing the Protocol](#ref0_TOC)**

After DCP approves the concept, the next step is to develop a draft protocol, patient reported outcomes, and case report forms, with a deadline to submit a clean protocol to DCP. The investigator is normally given **90 days** to draft the first full version of the protocol.

1. Protocol and forms development is a team effort.
There will be a few milestones in the protocol and forms development process, which includes a 4-hour RAPID call and a review by the Statistical Center Protocol Review Committee (PRC).

*RAPID Call structure:*

Introductions

Purpose of RAPID

Go through conflicts/problems first

Go through protocol page by page

Go through informed consent page by page

Go through forms page by page

*Statistical Center Protocol Review Committee:*
The statisticians and data coordinators will review a version of the protocol that is farther along in development and reflects the version that the NCI will review. They also review the protocol and forms as well.

After all of these materials have been scientifically approved by DCP, the materials need to be approved by the Central IRB prior to protocol activation.

**[Investigator Applies for a NIH Grant and Lists SWOG as a Subcontractor](#ref0_TOC)**

**Overview**
Investigator sometimes submits a NIH grant through his/her home institution to cover a study’s costs, such as non-standard of care testing or other site-related costs. In order for these study-related funds to be passed through to participating SWOG member sites, costs need to be included into a planned subcontract. The planned subcontract will be executed by SWOG’s fiduciary home institution, which is Oregon Health and Science University (OHSU). OHSU has an agreement in place with all SWOG sites that participate in clinical studies. The agreement says SWOG (via OHSU) will facilitate payments to the sites for their participation in the study.

**How to Apply**Investigator will work with his/her home institution’s sponsored research staff and office. Early in the grant development process a conference call should be set up that includes the SWOG committee co-chairs, the investigator, the investigator’s grant manager, and the SWOG federal budget staff to foster an understanding of the time-line and types of things that need to be considered in the grant. An on-going collaboration between the investigator’s grant manager and SWOG’s budget person should continue after the call to facilitate the development and review of a subcontract budget that includes clinical trial and administrative costs. The SWOG contact can also facilitate a letter of support from the Group Chair on behalf of the application for federal support.

**Contact**

|  |  |  |
| --- | --- | --- |
| SWOG Contact | Patricia Mize, SWOG’s Research Contracts and Grants Manager | mizep@ohsu.edu |
| Secondary Contact | Casey Dawson, Assistant Director of Administration | dawsoca@ohsu.edu |

**[Clinical Trials Initiative (CTR) Contracts: Administering Non-Federal Dollars to Cover Study-Related Costs](#ref0_TOC)**

**Overview**Investigator sometimes learn that a collaborating pharmaceutical company or other entity is interested in partnering with SWOG on the study and in covering clinical trial costs that cannot be charged to SWOG’s federal grants. These costs could be non-standard of care patient testing or procedures (i.e. biopsies), site related costs, human tissue banking, translational medicine research, patient reported outcomes, or quality of life research.

The costs could also cover the provision of a drug, nutraceutical or product to be investigated in the study. If such a relationship exists, SWOG will partner with the investigator to develop a budget and negotiate a contract with the entity. All non-federal dollars are administered through SWOG Clinical Trials Initiative (SWOG-CTI), a limited liability corporation housed within SWOG’s Foundation (The Hope Foundation). In the case of site related costs, SWOG-CTI has an agreement in place with all SWOG sites that participate in the clinical study. The agreement says SWOG-CTI will pay the site for its participation in the study.

**How to Apply**As with federal grants, early in the budget development process a conference call should be set up that includes the SWOG committee co-chairs, the investigator, and the SWOG-CTI budget and contracting staff to foster an understanding of the timeline and types of things that need to be considered in the budget and contract.

Investigators will work with Casey Dawson to develop a comprehensive budget for submission to the partnering entity. The investigator should not submit the budget on his own but only through SWOG. An ongoing collaboration between the investigator and SWOG-CTI’s budget person should continue after the call to facilitate the development and review of a contract budget that includes the clinical trial and administrative costs.

A determination of an IND (investigational new drug) will be made in consultation with the pharmaceutical company, with the final determination made by SWOG. The Group will contact the FDA if necessary. Please note that the investigator and his/her institution are not parties to this contract. If the partnering entity requests a confidential disclosure agreement (CDA), SWOG will help to facilitate, but the CDA will need to be executed with the investigator and his/her institution.

**Clinical Trials Initiative Contacts**

|  |  |  |
| --- | --- | --- |
| SWOG Budget Contact | Casey Dawson, Assistant Director of Administration | dawsoca@ohsu.edu |
| SWOG Contract Contact | Edie Van Putten, JD, Contract Attorney  | vanputte@ohsu.edu |

**[Nationwide: Services and Storage for Biospecimens](#ref0_TOC)**

 **Overview**

SWOG partners with Nationwide Children’s Hospital Biopathology Center, which is funded by a separate NCI grant and provides basic banking services and storage for all types of biospecimens in Phase III and randomized Phase II treatment trials; however, DCP studies do not automatically benefit from these banking services. Occasionally, there is supplemental funding made available for banking services needed in Division of Cancer Prevention (DCP) studies.

Because DCP studies do not automatically benefit from these banking services, the need for biobanking services and storage becomes an important discussion topic early in a study development. SWOG is prepared to partner with investigators, their committee chairs and executive officers to develop a budget for banking services, and to provide help and direction in seeking funding for this important resource and service. In the DCP setting, banking services that may require a budget include:

* banking services (operations)
* receipt and processing of specimens from Phase III and Phase II trials
* providing histology services related to quality control
* tissue quality evaluation
* equipment and supplies
* storage costs
* costs for informatics to track specimens
* banking services like cell separation, DNA extraction, specimen shipping costs to labs, tissue microarrays, etc.
* special supplies such as cell stabilization tubes or specialized tissue collection kits
* central pathology review

**How to Apply**

Early in the grant development process a conference call should be set up that includes the committee co-chairs, the investigator, and SWOG staff to discuss the need for banking services that may be required for the study. Depending on the results of this discussion, a budget and request for funding can be developed along the appropriate funding avenue whether it be an R01 grant, collaboration with a partnering entity, a request to DCP submitted on your behalf by the Group Chair, or an application to a Hope foundation clinical trial support program.

**Contact**

|  |  |  |
| --- | --- | --- |
| SWOG Contact | Casey Dawson, SWOG’s Assistant Director of Administration | dawsoca@ohsu.edu |
| Direct Contact  | Kae Tegtmeier, Program Manager, Operations/BCR Logistics | Kae.Tegtmeier@nationwidechildrens.org |
| Secondary Contact | Nathan Eriksen, SWOG’s Chief of Administration | eriksen@ohsu.edu |

**[SWOG Trial Support (STrS)](#ref0_TOC)**

**Overview**
The SWOG Trial Support (STrS) program seems particularly well suited to support certain aspects of DCP studies that do not otherwise have support from the SWOG grants or an outside source. The program was established to ensure that outstanding proposals don’t languish for lack of financing. STrS is designed to support study components that need supplemental funding during patient enrollment. Qualifying components may include things that are outside of the normal SWOG-support; however, STrS does not cover biomarker analyses, salary support or travel for investigators. The award will provide up to $75,000 per year for up to two years for approved and activated SWOG studies. Investigators may apply for STrS support at the same time they submit concept for SWOG Executive Review (Triage). The appropriate Committee Chair and Executive Officer should first review the STrS request for suitability. During the Triage Review call, the STrS request will be reviewed alongside the concept and any translational medicine components, applying two primary criteria:

* Impact score of the parent clinical trial
* Significance of the STrS component to the overall trial
* STrS application materials can be found here:
<http://thehopefoundation.org/research-funding/juried-programs/swog-trial-support-strs/>

**How to Apply**

Early in the study development process a conference call should be set up that includes the committee co-chairs, the investigator, and SWOG staff to discuss the need for services that may include an application to a Hope Foundation program. Depending on the results of this discussion, a budget and request for funding can be developed in partnership with the investigator. In most cases, this work should take place prior to Triage Review, as the STrS request will be reviewed along with the concept.

|  |  |  |
| --- | --- | --- |
| SWOG Contact | Casey Dawson, SWOG’s Assistant Director of Administration | dawsoca@ohsu.edu |
| Direct Contact | Johanna Horn, President, The Hope Foundation | jo@thehopefoundation.org |
| Secondary Contact | Nathan Eriksen, SWOG’s Chief of Administration | eriksen@ohsu.edu |

**[Division of Cancer Prevention (DCP) Funds](#ref0_TOC)**

 **Overview**

Under the right circumstances, SWOG executive leadership may decide to appeal to the Division of Cancer Prevention (DCP) program officers to request a funding supplement to support some specific aspect(s) of a study. This most often occurs when the study has been identified as a high priority study during the study’s early development phase. Sometimes DCP program managers have been participants in such early development discussions, and have invited SWOG or its investigators to submit such a request.

**How to Apply**

Early in the trial development process a conference call should be set up that includes the committee co-chairs, the investigator, and SWOG executive staff to discuss the possibility of a supplement request. Depending on the results of this discussion, a budget and request for funding can be developed in partnership with the investigator. While there is no specific timeline for this type of request, it is beneficial to identify the needs and submit the request as early as possible in the study development process, but only after there is a clear indication that the study will be given a warm reception by DCP. As such, some initial conversations are usually necessary with DCP program managers.

**Contact**

|  |  |  |
| --- | --- | --- |
| SWOG Contact | Patricia Mize, SWOG’s Research Contracts and Grants Manager | mizep@ohsu.edu |
| Secondary Contact | Casey Dawson, SWOG’s Assistant Director of Administration | dawsoca@ohsu.edu |

[**Biomarker, Imaging, and Quality of Life Studies Funding Program (****BIQSFP)**](#ref0_TOC) **Overview**
SWOG is invited to apply for funding to BIQSFP Program to support biomarker, imaging, and quality of life studies with or without cost-effectiveness analysis (CEA) proposals which are associated with NCI clinical trial concepts. Integral and/or integrated studies associated with Phase 3 treatment trials and cancer prevention trials are eligible. Only randomized Phase 3 clinical trials are eligible for CEA proposals. Support of Phase 2 clinical trials is limited to large (≥ 100 patients), randomized treatment trials with an integral and/or integrated biomarker or imaging studies). <http://www.cancer.gov/about-nci/organization/ccct/other-programs/biqsfp>

* BIQSFP may support biospecimen and tissue procurement, shipping costs, and analysis if the results are integral to the stated primary or secondary objectives of the approved trial. It is recommended that these questions be discussed with CTEP or DCP Program Staff prior to protocol submission to determine eligibility.
* BIQSFP may support Integrated QOL/PRO study applications. These must be submitted after parent concept approval but prior to protocol activation. Subsequent NCI prioritization and approval for funding will be decided by CTROC after evaluation of the QOL/PRO study by DCP and the respective NCI Steering Committee (SC), if applicable.
* BIQSFP may support cost-effectiveness analysis (CEA). The investigator must explain why it is necessary to conduct CEA alongside the parent clinical trial. For example, explain why an independent modeling study conducted during or after a clinical trial has been completed is not feasible, and/or why it would be of lesser value in informing clinical practice and/or policy compared to a CEA conducted alongside the parent clinical trial.

**How to Apply**

Early in the trial development process, a conference call should be set up that includes the committee co-chairs, the investigator, and SWOG executive staff to discuss the possibility of a BIQSFP request. Depending on the results of this discussion, a budget and request for funding can be developed in partnership with the investigator. INTEGRAL study applications must be concurrently submitted with the Parent Concept, to the respective PIO (CTEP or DCP Protocol Information Office). INTEGRATED and CEA study applications must be submitted after parent concept approval but prior to protocol activation. It is beneficial to identify the needs to aid in the application development process. Initial conversations are encouraged with the NCI BIQSFP program managers. All BIQSFP applications must be submitted through the SWOG Group Chairs Office at Oregon Health and Science University (OHSU)

**Contact**

|  |  |  |
| --- | --- | --- |
| SWOG Contact | Patricia Mize, SWOG’s Research Contracts and Grants Manager | mizep@ohsu.edu |
| Secondary Contact | Casey Dawson, SWOG’s Assistant Director of Administration | dawsoca@ohsu.edu |

**[The Hope Foundation](#ref0_TOC)**
**Overview**
SWOG established The Hope Foundation in 1993 to serve as the charitable arm of the group. The Hope Foundation provides fellowships and research grants, educational programs, Group Meeting support, and professional development for SWOG‘s network of cancer researchers. There are several programs designed to support specific areas/forms of research and investigator training.

**How to Apply**

These programs can be reviewed at <https://thehopefoundation.org/research-funding/>

|  |  |  |
| --- | --- | --- |
| SWOG Contact | Johanna Horn, President, The Hope Foundation | jo@thehopefoundation.org |

**[SWOG NCORP Contact List](#ref0_TOC)**

|  |
| --- |
| **SWOG NCORP Contact List****Last Updated: 1/22/19** |
| **Cancer Care Delivery Research Committee** |
| Gary Lyman, MD, MPH\* | Executive Officer | glyman@fredhutch.org |
| Dawn Hershman, MD, MS\* | Co-Chair, NCORP Vice-Chair | dlh23@columbia.edu |
| Scott Ramsey, MD, PhD | Co-Chair | sramsey@fredhutch.org |
| Barbara Segarra-Vazquez, PhD | Advocate | barbara.segarra@upr.edu |
| William Barlow, PhD | Primary Statistician | williamb@crab.org |
| Joseph Unger, PhD\* | Primary Statistician | junger@fredhutch.org |
| Patricia O'Kane\* | Protocol Coordinator | pokane@swog.org |
| **Cancer Survivorship Committee** |
| Katherine Crew, MD, MS\* | Executive Officer | kd59@columbia.edu |
| Melinda Irwin, PhD, MPH | Co-Chair |  melinda.irwin@yale.edu |
| Halle Moore, MD | Co-Chair | mooreh1@ccf.org |
| Lee Jones, MBA | Advocate |  lee-jones@verizon.net |
| Katherine A. Guthrie, PhD\* | Primary Statistician | kguthrie@fredhutch.org |
| Vanessa Garcia\* | Protocol Coordinator | vgarcia@swog.org |
| **Prevention and Epidemiology Committee** |
| Katherine Crew, MD, MS\* | Executive Officer | kd59@columbia.edu |
| Banu Arun, MD | Co-Chair | barun@mdanderson.org |
| Marian Neuhouser, PhD | Co-Chair | mneuhous@fredhutch.org |
| Cheryl Jernigan | Advocate | callcjjj@aol.com |
| Garnet Anderson, PhD | Primary Statistician | garnet@whi.org |
| Patricia O'Kane\* | Protocol Coordinator | pokane@swog.org |
| **Symptom Control and Quality of Life Committee** |
| Gary Lyman, MD, MPH\* | Executive Officer | glyman@fredhutch.org |
| Michael Fisch, MD | Co-Chair | fischm@aimspecialtyhealth.com |
| Norah Lynn Henry, MD, PhD | Co-Chair | lynn.henry@hci.utah.edu |
| Amy Geschwender, PhD | Advocate | amy.geschwender@licor.com |
| Joseph Unger, PhD\* | Primary Statistician | junger@fredhutch.org |
| PRO Development Team | K Arnold, A Darke, J Unger, R Vaidya, M Yee | PRO@crab.org |
| Sandi Jo Hita | Protocol Coordinator | sjhita@swog.org |
| **Palliative Care and End-of-Life Committee** |
| Katherine Crew, MD, MS | Executive Officer | kd59@columbia.edu |
| Robert Krouse, MD | Co-Chair | robert.krouse@va.gov |
| Mark O’Rourke, MD | Co-Chair | MORourke@ghs.org |
| Marie Bakitas, DNSc, NP-C, FAAN | Co-Chair | mbakitas@uab.edu |
| Valerie Fraser | Adovcate | valeriefraser@gmail.com |
| Katherine A. Guthrie, PhD | Primary Statistician | kguthrie@fredhutch.org |
| Vanessa Benavidez\* | Protocol Coordinator | vbenavidez@swog.org |
| **Operations, Administration, Grants and Contracts Staff** |
| Dana Sparks, MAT | Director of Operations and Protocols | dsparks@swog.org |
| Gretchen Goetz\* | Protocol Operations Manager | ggoetz@swog.org |
| SWOG Membership Department | Connie Barnes, Leslie Weissenstein, Tiffin Despres | member@swog.org |
| Nathan Eriksen | Chief of Administration | eriksen@ohsu.edu |
| Casey Dawson | Assistant Director of Administration | dawsoca@ohsu.edu |
| Pat Mize | Grants and Contracts Director | mizep@ohsu.edu |
| Edie Van Putten, JD | Contracts Attorney | vanputte@ohsu.edu |
| Tristan Parker, JD | Contracts Attorney | parketr@ohsu.edu |
| **The Hope Foundation** |
| Johanna Horn | President | jo@thehopefoundation.org |
| Morgan Cox | Grants and Communications Administrator  | morgan@thehopefoundation.org |
| **Statistics and Data Management Center Staff** |
| Kathryn Arnold, MS | Statistician  | karnold@fredhutch.org |
| Amy Darke, MS | Statistician  | adarke@fredhutch.org |
| Danika Lew, MA | Statistician | dlew@fredhutch.org |
| Edward Mayerson, MS | Statistician | emayerson@fredhutch.org |
| Anna Moseley, MS | Statistician  | amoseley@fredhutch.org |
| Riha Vaidya, PhD | Staff Scientist | rrvaidya@fredhutch.org |
| Jennifer Maeser, MS | Recruitment and Retention Specialist | jenniferm@crab.org |
| Heidi Dong | Data Coordinator  | heidid@crab.org |
| Diane Liggett, CCRP | Data Coordinator  | dianel@crab.org |
| Jennifer Patterson | Data Coordinator  | jenniferp@crab.org |
| Roxanne Topacio, CCRP | Data Coordinator  | roxannet@crab.org |
| Monica Yee, CCRP\* | Program Director, Cancer Control Studies  | monicay@crab.org |
| **NCORP Vice-Chair Office Staff** |
| Cynthia Law, MPH\* | Project Manager | cwl2129@cumc.columbia.edu |

 \**NCORP Executive Review Committee Member*

**[SWOG CONCEPT/CAPSULE SUMMARY FOR DCP STUDIES](#ref0_TOC)**

|  |  |
| --- | --- |
| Study Title: |  |
| Date of ERC Submission: |  |

**Section I**

|  |  |
| --- | --- |
| 1. **Study Characteristics**
 |  |
| * + 1. Study Phase:
 | I | II | III | Other  |
| * + 1. Randomized?
 | Yes | No |
| * + 1. Accrual goal
 |  |
| * + 1. Will data be used to support a new drug or device indication?
 | Yes | No |

|  |  |  |
| --- | --- | --- |
| 1. **Study Components**
 | **Yes** | **No** |
| * an investigational drug/compound?
 |  |  |
| * investigational diagnostic test/assay?
 |  |  |
| * an investigational device?
 |  |  |
| * patient reported outcomes (such as PRO-CTCAE, PROMIS, QOL etc)?
 |  |  |
| * a cost effectiveness component?
 |  |  |
| * biospecimen collection and banking?
 |  |  |

|  |
| --- |
| 1. **Disease and Research Committee Sponsorship**
 |
| 1. Primary SWOG Committee:
 |  |
| 1. Secondary SWOG Committee\*:
 |  |

\*Note:

* if any patient reported outcomes (PRO’s) are planned, the Symptom Control and QOL committee must be included as a secondary committee (if it is not the primary committee)
* if cost effectiveness studies are included, the Cancer Care Delivery committee must be included as a secondary committee (if it is not the primary committee)

|  |
| --- |
| 1. **Administrative Committee or Working Group Involvement:**
 |
| Yes | No | 1. Does the study involve/include:
 | Yes\*\* | No | 1. Additional Participation in Capsule:
 |
|  |  | 1. surgery/surgical evaluation?
 |  |  | 1. Surgery Committee
 |
|  |  | 1. radiation therapy?
 |  |  | 1. Radiation Therapy Committee
 |
|  |  | 1. imaging endpoints? (ie RECIST)
 |  |  | 1. Imaging Committee
 |
|  |  | 1. SWOG international sites?
 |  |  | 1. International Working Group
 |
|  |  | 1. adolescents and young adults?
 |  |  | 1. Adolescent and Young Adult Committee
 |

\*\* if yes, then the committee chair sign-off date should be included on the final capsule page.

|  |  |
| --- | --- |
| 1. **Study Chair information**
 |  |
| 1. Name and Degree:
 |  |
| 1. Institution :
 |  |
| 1. Study Chair Workshop completed date:
 |  |
| 1. YITC Course Attendance :
 | Yes | Year | No |

1. **Committee Prioritization (to be filled out by the primary SWOG Disease and Research Committee Chair)**

|  |
| --- |
| A. List all Executive Review Committee (ERC)- approved studies in development in the Primary SWOG Committee, in rank order of priority: |
| 1. |
| 2. |
| 3. |

|  |
| --- |
| B. List/describe actively recruiting studies in the same or similar patient population, with current accrual and planned closure date, including SWOG, NCTN, and industry trials. |
| 1. |
| 2. |
| 3. |

|  |
| --- |
| C. Primary committee chair: Please provide a paragraph summarizing your assessment of the potential future impact of this trial on patients - including whether the results will be impactful if the trial is either “negative” or “positive” |
|  |

|  |
| --- |
| D. Primary committee chair: Please describe any known connections of the science of this trial with research being performed in NCI supported Cancer Centers, SPORES, or R01’s (this information will be used to support SWOG’s future grant renewals). |
|  |

**Section II:** **How to Develop a DCP Concept** **from a Study Idea into a Scientific Research Plan**

# A concept should have been reviewed and approved by all necessary components at the Research Base before submission to DCP. Although not a full protocol, the concept should provide sufficient information to establish the scientific rationale for the proposed study, describe the study methodology, and support the feasibility of conducting a successful study. Concepts do not need to include consent forms or case report forms, although they should include (as appendices) all of the questionnaires or measurement instruments to be used for the primary endpoint. Concepts may be no longer than 10 pages in length, excluding the title pages, references, and appendices.

# Although DCP does not mandate the use of a set template for concepts, it does require specific information to be included in all study concepts. This information includes:

***Concept Content***

1. Title Page – This is the primary source of identifying information for DCP PIO. Each concept must have a title page that contains:

### Date of document

### Local concept number (i.e., institution or group number)

### Title of study

### Clear identification as a clinical trial or cancer care delivery research study

### Identified study personnel responsible for the study, including name, institution, address, phone and fax numbers, and email address:

#### single study chair

#### co–chair(s)

#### related committee chairs

#### primary statistician

### f. Full name of Research Base submitting the study

### g. For agents requested from DCP, a listing of each agent by name and Cancer Chemotherapy National  Service Center number (NSC Number)

#### Background – This is the most important section of the concept, as it provides reviewers the rationale and scientific justification for conducting the study. It should contain:

1. A detailed rationale for the study:

a. What is the current state of knowledge or clinical/care delivery practice? Include preclinical, clinical and/or pilot data that support conducting the study

b. What research gap is being addressed?

c. What is the clinical relevance/significance of the problem under study?

d. How is the study intervention novel?

e. For randomized, symptom intervention studies, what priority research area identified by the Steering Committee and Research Base does the study address? If not a priority research area, what is the justification for the area of research proposed?

f. What will this study contribute to cancer prevention, control, or screening/post treatment surveillance or care delivery? Although other contributions are important and should be included, this section should explain how information from the study would affect care of patients or the delivery of cancer care.

g. Why is the study design the best way to make this contribution?

h. Include information about the study population and intervention; the study populations could include patients, clinicians and/or organizations.

i. How will this research affect subsequent research?

j. How will the research inform patient care/improve patient outcomes?

k. Why were the endpoints chosen?

2. A literature review (a focused review of relevant literature with citations), which should cover:

a. Current knowledge

b. Other studies that have contributed information applicable to the study

c. Information on drugs, procedures and measurement instruments to be used

d. Other information justifying the research and its methodology:

3. Information related to feasibility:

a. State if NCORP Community Sites and Minority/Underserved Community Sites have been involved in developing or reviewing the concept

b. What is level of interest expressed by NCORP sites and how this information was elicited?

c. Note level of anticipated participation and accrual from NCORP sites and other members

d. Provide any additional data or information to support the anticipated accrual or participation rate

e. Specify procedures for recruitment and retention of participants (if applicable) including minority and underserved populations

f. If the study will involve costs in addition to data management, describe them and include a source of funding

g. Describe the time commitment of patients, research staff, physicians or other study participants

h. For cancer care delivery research studies, provide information on the anticipated availability of organizational, financial and other administrative data

C. Study Objectives

D. Study Design, including:

#### Schema: This one-page diagram provides an overview of the study design. To be most useful, it should include:

###### Sample size

###### Study population

###### Stratification factors

###### Study design (e.g. randomization, case controlled, observational)

###### Specific intervention(s) (with dose, timing of data collection, etc.) if applicable

###### Eligibility criteria and characteristics of study population

###### Clear definitions of the primary and secondary endpoints

###### Stratification factors and justification for using them

###### Detailed description of the intervention if applicable (including, for drugs, the provider; for complementary and alternative treatments, information on quality control and content; for behavioral or organizational interventions, the availability of resources in the community setting to provide the intervention, for procedural interventions, the willingness of the study populations to implement; for practitioner/organizational interventions, the availability of participants)

###### Detailed description of the outcome measure(s) used included reliability and validity for the disease and patient population under study

###### Study Calendar or Study Parameters Table outlining the tests and observations to be performed and the timing of them

###### For pharmaceutical agents, including complementary and alternative agents:

###### Describe how agent will be provided, supported and assessed for quality control

###### Document plan to submit protocol to FDA for IND review

###### For behavioral and organizational interventions:

###### Describe availability of resources in community setting to provide intervention

###### Document plan to train community sites to provide intervention

###### Detailed methodology and explanation regarding how sub-studies (if applicable) will contribute useful information relevant to specified hypotheses.

###### If biomarkers are included, state rationale for use and whether they are validated.

###### Include funding source for biomarker collection, testing and storage

###### E. Statistical analyses plan, including:

###### Hypothesis

1. Define study endpoints including how and when they will be measured
2. Sample size calculation

###### Estimated effect size

1. Justify choice of effect size and include power analysis
2. Estimate of drop-outs/loss to follow-up

###### Plan for handling missing data

###### Plan for analyzing the primary endpoint

###### Timing of data collection

###### Analysis plan for all sub-studies (if applicable)

###### Plans for addressing data limitations (if applicable)

###### Description of how the statistical significance translates to a significant difference clinically.

1. Translational Medicine (check all that apply)

|  |  |  |
| --- | --- | --- |
|  | 1. Integral TM
 | Translational medicine studies that will be included in the clinical protocol are required for study eligibility, stratification assignment or treatment decision.  |
|  | 1. Integrated TM
 | Translational medicine studies that will be included in the clinical protocol are required for assessment of the primary study endpoint; OR: samples are required to be tested in real-time, due to degradation  |
|  | 1. Banking only
 | Specimen collection for banking will be included in anticipation of future TM research.  |
|  | 1. No TM
 | Specimen collection is not required/requested. |

Notes:

* If there is integral or integrated TM, a “Proposal for an Integral or Integrated Translational Medicine Study” MUST accompany Capsule Summary submission and a funding plan should be described.
* Funding for specimen banking is available for Phase III and randomized Phase II clinical trials within the Disease and Research committees. For banking in other studies, alternate funding will likely be required.

**Section III: Resource Plan**

1. Anticipated needs
2. Drugs/Agents: Please list detail

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Agent Name | Request for CTEP/PMB-distribution? | Is the agent Investigational? | Who is the IND Holder? | NSC Number[[1]](#footnote-1) | Placebo Controlled? |
|  | ☐Yes ☐No | ☐Yes ☐No  | ☐Company ☐Consortium ☐CTEP ☐Group ☐Investigator☐Other (Specify):\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ |  | ☐Yes ☐No  |
|  | ☐Yes ☐No | ☐Yes ☐No  | ☐Company ☐Consortium ☐CTEP ☐Group ☐Investigator☐Other (Specify):\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ |  | ☐Yes ☐No |
|  | ☐Yes ☐No | ☐Yes ☐No  | ☐Company ☐Consortium ☐CTEP ☐Group ☐Investigator☐Other (Specify):\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ |  | ☐Yes ☐No |
|  | ☐Yes ☐No | ☐Yes ☐No  | ☐Company ☐Consortium ☐CTEP ☐Group ☐Investigator☐Other (Specify):\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ |  | ☐Yes ☐No |
|  | ☐Yes ☐No | ☐Yes ☐No  | ☐Company ☐Consortium ☐CTEP ☐Group ☐Investigator☐Other (Specify):\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ |  | ☐Yes ☐No |
|  | ☐Yes ☐No  | ☐Yes ☐No  | ☐Company ☐Consortium ☐CTEP ☐Group ☐Investigator☐Other (Specify):\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ |  | ☐Yes ☐No |

1. Procedures: Please list any medical procedures, etc. that the patient must undergo for eligibility, therapy, safety, and/or primary endpoint measurements that are NOT standard of care (ie blood work, imaging procedures, biopsies, etc).

|  |  |  |
| --- | --- | --- |
| Procedure | Rationale | #Episodes/patient  |
|  |  |  |
|  |  |  |
|  |  |  |
|  |  |  |

1. Data Collection: Please list any data collection items that are necessary for study performance that are not SWOG norm (eg,, PRO’s, submission of insurance/claims data, central imaging review, central pathology review).

|  |  |  |
| --- | --- | --- |
| Data requirement | Rationale | #Episodes/patient  |
|  |  |  |
|  |  |  |
|  |  |  |
|  |  |  |

1. International Participation: Please describe the scope of the anticipated international participation, if any.

|  |  |  |
| --- | --- | --- |
| Country or Network | Mechanism (ie, SWOG member, consortium, etc) | # accruals  |
|  |  |  |
|  |  |  |
|  |  |  |

1. Anticipated Support
2. Commercial Support
	1. Please list any anticipated commercial partnerships for this study.

|  |  |
| --- | --- |
| Name of company (1) |  |
| Name and title of contact individual: |  |
| Address: |  |
| Phone: |  |
| Fax: |  |
| Email: |  |

|  |  |
| --- | --- |
| Name of company (2) |  |
| Name and title of contact individual: |  |
| Address: |  |
| Phone: |  |
| Fax: |  |
| Email: |  |

|  |  |
| --- | --- |
| Name of company (3) |  |
| Name and title of contact individual: |  |
| Address: |  |
| Phone: |  |
| Fax: |  |
| Email: |  |

* 1. Do you anticipate that the commercial entity or entities will provide support for:

|  |  |  |  |
| --- | --- | --- | --- |
| NO | YES | N/A | SUPPORTED ITEM |
|  |  |  | New drug or device indication data collection and transfer in IA4 |
|  |  |  | Integral or integrated TM studies (laboratory assays) in IIB |
|  |  |  | Biospecimen banking in IIB |
|  |  |  | Investigational or commercial drug(s) in IIIA1 |
|  |  |  | Drug distribution in IIIA1 |
|  |  |  | Non-standard of care clinical procedures (including imaging, biopsies, etc) in IIIA2 |
|  |  |  | Non-standard data collection items in IIIA3 |
|  |  |  | International participation in IIIA4 |
|  |  |  | Other (please write in) |

1. Grant Support
	1. Are any grants planned to support aspects of this study, such as BIQSFP, R01, SWOG/THF Impact Award, ITSC grants, SWOG Trial Support (STrS)\*\*?

|  |  |  |
| --- | --- | --- |
| Grant type: | Submission deadline: | Funding start date (approx.) |
|  |  |  |
|  |  |  |
|  |  |  |
|  |  |  |

\*\*if STrS is requested, include one page application with ERC submission

DEADLINES:

The targeted timeframe for activating Phase II studies is 210 days (measured from CTEP LOI submission to first IRB approval). The targeted timeframe for activating Phase III studies is 300 days (measured from CTEP Concept submission to first IRB approval.) Please list all issues or concerns that may hamper this study’s ability to meet these timelines:

**Section IV: SWOG Protocol Coordinator Section**

Please indicate when the following role representatives approved submission of the capsule to Executive Review Committee.

|  |  |  |
| --- | --- | --- |
| REVIEWER ROLE | Date of Review | Reviewer Name |
| Study Chair |  |  |
| Primary Scientific Committee Statistician |  |  |
| Primary Scientific Committee Chair |  |  |
| Primary Scientific Committee TM Vice Chair\*  |  |  |
| Secondary Scientific Committee Chair(s)\*\* |  |  |
| Primary Scientific Committee Exec Officer |  |  |
| Primary Scientific Committee Patient Advocate  |  |  |

\* if integral/integrated studies are planned

\*\*Note:

1. if any patient reported outcomes are planned, review by the Symptom Control and QOL committee is required
2. if cost effectiveness studies are included, review by Cancer Care Delivery committee is required

### **[Example: 1-Page Write Up](#ref0_TOC)** *Concept begins as a study idea in a 1-page write up.***Text Messaging Intervention To Improve Cardiovascular Health In Breast Cancer Survivors**

**Hershman, DL; Crew KD**

**Background:** Due to early detection and improved treatments, women with breast cancer (BC) are living longer. While breast cancer-specific mortality has been steadily decreasing in recent years due to improvements in treatment, deaths due to other causes account for 60%-83% of overall mortality in breast cancer survivors. Recent studies show that patients diagnosed with early-stage invasive breast cancer are more likely to die from CVD than breast cancer. A population-based study that followed 36,000 adult cancer survivors up to 8 years found a 13% increase in CVD incidence rates among breast cancer survivors compared to age-sex-matched non-cancer controls. Survivors who developed CVD had significantly lower 8-year survival rates than those without CVD. Guidelines for cardiovascular risk reduction overlap with survivorship guidelines for breast cancer patients.

Our group and others have shown that adherence to CVD medications, such as statins and diuretics, is poor in breast cancer survivors, particularly during the period of breast cancer treatment and in the year following diagnosis. Non-adherence to physician treatment recommendations is an increasingly recognized cause of adverse CVD outcomes in older adults with cardiovascular disease. Previous studies suggest that higher adherence to CVD medications is significantly associated with fewer cardiovascular events.

A recently reported randomized trial of a semipersonalized support program delivered by mobile text messages found that that a simple, low-cost automated program led to significant reductions in LDL-C level, systolic blood pressure, and BMI in patients with CHD. Intervention participants were also substantially more likely to exercise regularly and become nonsmokers. There was a high level of acceptability of the intervention, with an overwhelming number of participants in the intervention group perceiving the messages to be of use and the level of contact to be appropriate.(Chow et al, JAMA, 2015).

**Design/intervention:** For this current proposal, we will conduct a multicenter randomized controlled trial to examine the effect of a semipersonalized support program delivered by mobile phone text message on cardiovascular risk factors in 750 post-menopausal breast cancer survivors who had at least 2 cardiovascular risk factors at diagnosis and have completed primary therapy. The intervention will be modeled after the above mentioned “TEXT-ME” study. Participants will receive 4 messages per week for 24 weeks, then 1 message per week for 24 weeks. Each message was sent on 4 of 5 randomly selected weekdays and arrived at random times of the day during working hours.

**Participants:** Post-menopausal women with a diagnosis of stage 1-3 breast cancer within 6-months of completing primary therapy (chemotherapy/radiation) who had a history of at least 2 personal cardiovascular risk factors prior to diagnosis. Cardiovascular risk factors include obesity, hypertension, diabetes, smoking, or a personal history of MI/CAD. Randomization will be stratified by use of cholesterol lowering medications.

**Outcome:** The primary end point will be low-density lipoprotein cholesterol (LDL-C) level at 6 months***.*** Secondary end points included systolic blood pressure, body mass index (BMI), physical activity, and smoking status, adherence to cardiovascular medications, adherence to breast cancer medications and acceptability of the intervention.

**Feasibility:** Based on our prior work in SWOG 1105, a text messaging study to reduce discontinuation of AI among women with breast cancer we feel confident we will be able to accrue 750 patients in 2.5 years. SWOG 1105 was a 3-year intervention, this study would be a 24 week intervention. That study accrued a similar number of patients in 18 months.

**[EXAMPLE: 10-Page Fully Developed Concept/Capsule](#ref0_TOC)**
*A fully developed concept as a 10-page write up. The fully developed concept corresponds to SWOG Concept/Capsule Summary From, Section II.*

Dawn Hershman, MD, MS

 Text Intervention to Improve Cardiovascular Health In Breast Cancer Survivorship
 Survivorship New Concept Submission

**Division of Cancer Prevention (DCP)
Survivorship New Concept Submission**

 **Date of Submission:** TBD

**Local Concept Number:** TBD

**Title:** Text Intervention to Improve Cardiovascular Health in Breast Cancer Survivors

**Study Chair:** Dawn L. Hershman, MD, MS

**Co-Investigators:** Katherine Crew, MD MS, Joseph Unger, MS, PhD

**Research Base**: SWOG

**Primary study objective:** To determine the efficacy of semi-structured support program delivered by mobile phone text 4 times a week for 24 weeks vs usual care on reducing LDL-C levels at 24 weeks in breast cancer survivors.

**Secondary study objectives:**

1. To evaluate the intervention’s efficacy compared to usual care with respect to:

	1. Systolic blood pressure, BMI, physical activity, and smoking status
	2. Adherence to adjuvant AI hormonal therapy and CVD medication
	3. Composite cardiovascular risk factor scores
	4. Biomarkers associated with both improved cardiovascular and breast cancer outcomes
2. To evaluate the efficacy of maintenance text compared to usual care with respect to:
	1. (1x/week) for an additional 28 weeks on LDL-C, systolic blood pressure, BMI, physical activity and smoking status at 52 and 104 weeks.
3. To estimate the cost-effectiveness of a text-messaging support program on reducing cardiovascular events and deaths from breast cancer based on improved drug adherence and reduced CVD risk factors.

**Hypothesis**: We hypothesize that exposure to a semi-personalized support program delivered by mobile phone text will improve drug adherence and reduce CVD/breast cancer risk factors, reducing Ischemic cardiovascular events and recurrence/mortality from breast cancer.

**Background:**

**Growing number of cancer survivors.** The number of cancer survivors in the U.S. has been rising steadily, with data from the National Cancer Institute (NCI) Office of Cancer Survivorship indicating a rise from 3.0 million in 1971 to >20 million in 20261 Breast cancer (BC) is the most common non-cutaneous malignancy among women, representing 4 in 10 female cancer survivors in the U.S.2 Through improvements in cancer detection and therapies (surgery, chemotherapy, hormonal therapy, targeted therapy, and radiotherapy), cancer survival has dramatically increased over the past few decades. This year, over 230,000 women will be newly diagnosed with BC, and an estimated 3.1 million BC survivors are alive in the U.S.The median age at diagnosis is 61 years, and 43% are older than 65 years at diagnosis; thus, cancer survivorship must be managed in coordination with comorbidities associated with aging.2 Approximately 61% will have localized disease, for which survival outcomes are highest (5-year survival rates: 99% for localized BC).1

**Cardiovascular disease risk factors and cardiac outcomes.** Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in the U.S., causing 1 of every 3 deaths each year. It is an economically burdensome disease, with CVD-related costs comprising 17% of the nation's total health expenditures.3 Efforts to reduce CVD and death have focused on primary and secondary prevention. There are several risk factors for heart disease. Abnormal lipids, smoking, hypertension, diabetes, abdominal obesity, psychosocial factors, decreased consumption of fruits, vegetables, and alcohol, and lack of physical activity account for most of the risk of myocardial infarction worldwide in both sexes and at all ages in all regions.4

**Breast cancer survivors are at increased risk of cardiovascular disease.** CVD is the leading cause for death in the general U.S. population and accounts for 35% of non-breast cancer-related deaths for BC survivors age 50 years or older.5 Recent studies show that breast cancer patients diagnosed with early-stage invasive breast cancer are more likely to die from CVD than BC.6 Observational studies suggest that CVD mortality starts to increase in breast cancer survivors 7 years after diagnosis,7 and becomes the leading cause of death in survivors 10 years after diagnosis.6 There are no known effective methods to prevent or treat cancer treatment-related cardiotoxicity.8,9 The prevention and treatment of CVD in cancer survivors is a priority area for the NCI and National Heart, Lung and Blood Institute (NHLBI).10

**Breast cancer treatment can increase the risk of cardiovascular disease.** Radiation, chemotherapy, and endocrine therapy with aromatase inhibitors (AIs) have been associated with an increased risk of CVD in patients with BC.11 The risk of heart disease increases in postmenopausal women, as endogenous estrogens in younger women contribute to the low prevalence of CVD in that population. Therefore, BC patients who experience treatment-related early menopause may be at higher risk for heart disease than age-matched women in the general population. The anthracyclines, such as epirubicin and doxorubicin, are associated with a low but real risk of cardiomyopathy12; similarly, trastuzumab is associated with an 4-fold risk of cardiac dysfunction, most notably when given concomitantly or after an anthracycline.8 Significant weight gain may lead to hypertension and insulin resistance, which further elevate the risk of CVD.

**Text messaging and Adherence.** A recent meta-analysis was conducted on mobile telephone text messaging for medication adherence in chronic disease (non-cancer). Sixteen randomized clinical trials were included, with 5 of 16 using personalization, 8 of 16 using 2-way communication, and 8 of 16 using a daily text message frequency. The median intervention duration was 12 weeks, and self-report was the most commonly used method to assess medication adherence. In the pooled analysis of 2742 patients, text messaging significantly improved medication adherence (OR, 2.11; 95% CI, 1.52-2.93). The effect was not sensitive to study characteristics (intervention duration or type of disease) or text message characteristics (personalization, 2-way communication, or daily text message frequency). The authors concluded that mobile phone text messaging approximately doubles the odds of medication adherence. This increase translates into adherence rates improving from 50% to 67.8%, or an absolute increase of 17.8%.13

**Adherence to endocrine therapy.** Lack of compliance (early discontinuation and/or non-adherence) with medications is a well-known problem for chronic conditions.62-64 Oral hormonal therapy for the adjuvant treatment of breast cancer results in a reduction in breast cancer recurrence,65 and for women at high risk for BC, these medications result in a 50% reduction in the incidence of new BC.66 We have shown that despite its efficacy, approximately 7-10% of patients discontinue hormone therapy annually,67-73 with only about 50% completing the recommended 5-year course. This non-adherence reduces the potential survival benefits.74-77

The reasons for non-adherence to hormonal therapy are multifactorial.78 Barriers to compliance include patient, physician, medication and system related variables and poor compliance is usually associated with a combination of these factors.79 Common findings include extremes of age, minority race, being single, increased number of comorbidities, prescriptions written by non-medical oncologists, number of total prescriptions, history of non-adherence to other chronic medications, insurance status, and higher out of pocket costs contribute to non-adherence.73,80-83 We recently reported that women who reported a better attitude toward endocrine therapy, better quality of life, and more treatment satisfaction, were less likely to be non-persistent and those who reported intrusive/avoidant thoughts were more likely to be non-persistent.84 These findings were used to develop a text-messaging intervention (S1105) for hormone therapy adherence which randomized over 700 women to receive text messages twice a week or usual care to improve adherence. The data are currently being analyzed.

**Text messaging can be effective at improving cardiovascular risk factors.** The TEXT-ME study found that a simple, low-cost automated program of semi-personalized mobile phone text messages supporting lifestyle change led to significant reductions in LDL-C level (−5mg/dL [95%CI, −9 to 0]), systolic blood pressure, and BMI in patients with CHD. Intervention participants were also substantially more likely to exercise regularly and become nonsmokers.14 Participants in the intervention group were more likely to control their blood pressure (relative risk [RR], 1.44; 95% CI, 1.29-1.61), exercise regularly (RR, 2.39; 95% CI, 1.92-2.97), and achieve nonsmoking status (RR, 1.33; 95% CI, 1.19-1.49). Intervention participants were more likely to achieve combined risk factor control; 28.9% of participants in the intervention group vs 10.3% in the control group achieved target levels for 4 or more risk factors (RR, 2.80; 95% CI, 1.95-4.02). The majority reported the messages to be useful (91%), easy to understand (97%), and appropriate in frequency (86%).

**R**

**A**

**N**

**D**

**O**

**M**

**I**

**Z**

**E**

**Usual Care**

**x 24 weeks**

**TEXT**

**4x/week x 24 weeks**

**TEXT**

**1x/week weeks (24-52)**

**Eligibility:**

 Female stage I-III BC

 ER/PR +

 Postmenopausal

 Has mobile phone

 2 cardiac risk factors or

 1+ if LDL >130

 Performance status 0-2

 No prior malignancy

**STRATIFY**: LDL<130

N=836

**Usual Care**

**Weeks**

**52-104**

**Usual Care**

**Weeks**

**52-104**

**Figure 1.** **Study schema**

**Research Plan:**

**Study Design and Objectives**

The study design (Figure 1) will be a randomized controlled trial in 836 postmenopausal women with a history of stage I-III breast cancer on AI therapy (given higher risk of CVD), with a previous history of modifiable cardiovascular risk factors (BMI, DM, HTN, Cholesterol, smoking) who will be →assigned to: 1) a 24-week semi-structured support program focused on lifestyle factors and drug adherence delivered by mobile phone text intervention 4 times a week for 24 weeks; or 2) →usual care. Maintenance will be examined weeks 24-52 by continuing with a weekly text message in the intervention group.

**Usual**

**Care**

**weeks (24-52)**

Both the usual care and intervention arms will receive a written summary of the ASCO/ACS breast cancer survivorship guidelines tailored to patients and patient centered information and weblinks from the American Heart Association (MyLifeCheck). Patients will be stratified by baseline LDL-C (<130 vs. ≥130mg/dl) and Framingham 10-year CVD risk (<10% vs. ≥10%). The primary endpoint is LDL-C at 24 weeks. We will also assess long-term changes in LDL-C at 52 and 104 weeks (1 year after the intervention). Other secondary outcomes include cardiac risk factors (systolic blood pressure, BMI, physical activity, smoking status), adherence to CVD medications and AI therapy, and blood biomarkers (insulin, glucose (to calculate homeostasis model assessment [HOMA]), HgbA1c, adiponectin, CRP). Participants will complete self-administered questionnaires and an assessment of medication adherence. Fasting blood collections for biomarker analyses and patient reported outcomes will occur at baseline, 24, 52 and 104 weeks.

**Eligibility**

Participants will be recruited from NCORP and NCTN sites and screened for the following eligibility criteria:

1. Postmenopausal women defined as the absence of menses for >12 months, serum FSH >20 mIU/ml, administration of a GnRH agonist, or history of bilateral oophorectomies. (Only women will be enrolled, since male breast cancer is rare and AIs are not the standard of care for men.)
2. Stage I-III hormone receptor-positive breast carcinoma without evidence of disease at trial entry.
3. Minimum of 3 months and maximum of 12 months since last chemotherapy, biologic therapy, radiation therapy, and/or breast surgery.
4. Patients must have a mobile phone that can receive text messages and must currently use or be willing to use or learn to use text messaging.
5. Current use of a third generation AI (anastrozole, letrozole, or exemestane) for a minimum of 1 month.
6. Presence of one of the following:
	1. 2 or more of the following cardiac risk factors prior to breast cancer diagnosis – diabetes, BMI ≥30 mg/m2, hypertension, hypercholesterolemia, coronary heart disease, current smoker (>1/week).
	2. 1 cardiac risk factor listed above prior to breast cancer diagnosis and fasting LDL-C ≥130 mg/dl within 3 months of registration.
7. ECOG performance status of 0, 1 or 2.
8. Able to complete self-administered questionnaires in English or Spanish.
9. No other prior malignancy is allowed except for adequately treated basal cell or squamous cell skin cancer, *in situ* cervical cancer, or other cancer for which the patient has been disease-free for >=5 years.
10. Must agree to provide fasting blood at the required time-points.
11. Signed informed consent.

**Study Intervention** The TEXT-ME intervention will be used and permission has been obtained from the investigators (see letter of support). The text message–based program involves delivery of regular semi-personalized text messages providing advice, motivation, and information that aimed to improve diet, increase physical activity, and encourage smoking cessation (if relevant). Content for each participant was selected using a pre-specified algorithm dependent on key baseline characteristics (smoking status, BMI, ect). A ‘bank’ of 100 text messages were developed and validated through an iterative process and based on national guidelines. The messages were categorized into four groups including: (1) general heart health information messages that include facts about CVD and information about medications and risk factors, (2) nutrition messages, (3) physical activity messages and (4) smoking cessation messages. The initial ‘bank’ of draft messages was scrutinized and modified by an expert review panel made up of a multidisciplinary group of clinicians (including cardiologists, a psychologist, a physiotherapist, nurses and public health specialists), researchers and academics. The final bank of text messages was evaluated by 53 consumers, who then completed a qualitative questionnaire. This survey asked for comment and feedback about usefulness and understanding for specific text messages.15 We will use the same intervention.

*Additional Message Content*

We will also use the text message content developed and implemented in S1105. Content themes focus on overcoming potential barriers to medication adherence and persistence and will include cues to action, statements related to the efficacy of the medication, reinforcements of the physician’s recommendation to take this medication, and words of support and encouragement (Table 1). Examples include “Putting up with side effects is worth it” and “Your doctor wants you to take this medication” or “Hormonal therapy is an important part of breast cancer treatment. You have much support from all of us in your efforts.” It has been repeatedly demonstrated in the literature that the physician is a trusted source of medical information and advice.

|  |
| --- |
| Table 1. TEXT ME Examples |
| General CVD Health |
| Remember- cholesterol and hypertension medications need to be taken daily |
| Not having support of family and friends can worsen heart disease |
| Check out http://www.heartfoundation.org |
| Nutrition |
| Try steaming or baking to reduce the need for excess oil when cooking |
| Healthy eating means five servings of vegetables every day |
| Smoking |
| It’s never too late to quit smoking |
| If you crave a cigarette try and distract yourself by going for a walk  |

**Participants randomized to the Control:** Both the intervention and control groups will get a written summary of the ASCO/ACS breast cancer survivorship guidelines tailored to patients and patient centered information and weblinks from the American Heart Association (MyLifeCheck).

**Baseline Data:**Information will be obtained on the patient’s primary breast cancer, tumor biology (stage, ER/PR status, Her-2 status), surgery (mastectomy/lumpectomy), chemotherapy (trastuzumab [Y/N]; anthracycline [Y/N]), radiation therapy (laterality, partial/whole breast). In addition, information on patients’ comorbid conditions, cardiac risk factors, and medication use will be collected.

**Self-Administered Questionnaires**

Demographic characteristics, health behaviors, current cigarette smoking and pack years, current medications, oral therapy adherence and medical history will be collected at baseline.

**Cell Phone and Text Messaging Use Questionnaire:** collects cell phone and text messaging use. (Only for patients randomized to receive text messaging)

**Drug Adherence Assessment:**We will assess overall medication adherence separately for hormonal therapy and CVD therapy (not adherence to specific medications) using 3 questionnaire items (endocrine and CVD medications individually) based on those used in the CARDIA (Coronary Artery Risk Development in Young Adults) study.16,17 (1) “In the past month, how often did you take your medications as the doctor prescribed?” Possible responses are all of the time (100%), nearly all of the time (90%), most of the time (75%), about half the time (50%), or less than half the time (<50%). Nonadherence is defined as 75% of the time or less. (2) “In the past month, how often did you forget to take 1 or more of your prescribed medications?” Possible responses were never, once in the past month, 2 to 3 times in the past month, once per week, several times per week, and nearly every day. Nonadherence is defined as forgetting to take prescribed medications once per week or more. (3) “In the past month, how often did you decide to skip 1 or more of your prescribed medications?” Possible responses were the same as for question 2. Nonadherence is defined as deciding to skip medications once per week or more. The first will be the primary measure of non-adherence.

We chose to measure self-reported medication adherence for several reasons. First, self-reported medication adherence has been validated as a reliable predictor of health outcomes, including blood pressure control,18 hospitalization for heart failure,19 and response to antiretroviral therapy.20 Second, in a study of hypertensive patients taking hydrochlorothiazide, self-reported medication adherence was more strongly correlated with qualitative urinary hydrochlorothiazide levels, changes in serum potassium levels, and decreases in blood pressure than was pill count adherence.48 Third, other methods of assessing adherence are not feasible for our study (pharmacy refill or Medication Event Monitoring).

**Treatment Satisfaction Questionnaire for Medication (TSMQ):** The 14-item TSQM Version 1.4 is a reliable and valid instrument to assess patients' satisfaction with medication, providing scores on four scales – side effects, effectiveness, convenience and global satisfaction. We will use the validated abbreviated TSQM-9.21 This will be used in the evaluation of medication adherence.

**IPAQ:**The International Physical Activity Questionnaire (IPAQ) is a well-validated tool that is used to assess health-related physical activity. The questionnaire contains 4 items which assess time spent engaging in physical activity in the 7 days prior to filling out the questionnaire. Specific activities that are assessed are walking, moderate-intensity activities, and vigorous-intensity activities. Patients are then classified as either having low, moderate, or high levels of physical activity.22

**PROMIS-29:**The Patient-Reported Outcomes Measurement Information System (PROMIS) 29 is a well-validated assessment tool that offers both qualitative and quantitative measures of health-related quality of life. The PROMIS-29 includes 29 questions evaluating areas of physical function, anxiety, depression, fatigue, sleep, social functioning, and pain interference. The PROMIS-29 assesses severity levels of symptoms and their effect on the patient’s functioning.

**Anthropometric Measures:** Height (cm), weight (kg), waist circumference (mm), hip circumference (mm).

**Cardiovascular Disease Risk Scores:** The assessment of CVD risk has been a key element in efforts to define risk factors, to identify and assess potential targets of therapy, and to enhance the cost-effective implementation of therapies for both primary and secondary prevention of CVD. We will use 2 common scores that have easy to use risk calculators and have been used in a variety of intervention trials

**Framingham 10-Year Coronary Heart Disease Risk Score (FR-10):** The Framingham Risk Score equation is a standard clinical tool used to predict the 10-year risk of coronary heart disease (FR-10) based on sex, age, total cholesterol, high-density lipoprotein (HDL) cholesterol, systolic blood pressure, and smoking, with the goal of its implementation being primary prevention of disease. The Framingham Risk equation has demonstrated utility for coronary heart disease risk prediction across diverse populations.23

**Life’s Simple 7:** In 2010, the Strategic Impact Goal statement from the American Heart Association defined a ‘new concept, cardiovascular health,’ which is measured using a seven-item composite score of modifiable health behaviors (smoking, physical activity, diet, and obesity) and clinical risk factors (blood pressure, total cholesterol, and fasting glucose).24 Each component has a threshold which is considered ‘ideal,’ *i.e.,* the most healthy classification. There are also intermediate and poor classifications. This new concept promotes primordial prevention, which is a preventative strategy that targets risk reduction at the population level by preventing risk factors for disease rather than the disease itself. The IDEAL may be more useful to show progress toward improved cardiovascular health from behavioral interventions and for populations with low short-term risk of coronary heart disease.25

**Blood Analyses:** Venous fasting blood samples will be obtained at baseline, 24 weeks (primary endpoint), 52 weeks (after maintenance text-messaging), and 104 weeks (a year after completion of the intervention).

At baseline, two 10 cc tubes of whole blood will be collected. Once the blood samples are received they will be immediately processed. Serum will be aliquoted into 1.0 mL and stored in a -80°C liquid nitrogen tank until analysis. Samples will be shipped within 24 hours of collection to maintain the integrity of the biospecimens.

For the biomarker analysis, LDL, HDL, Total Cholesterol, HbA1c, CRP, and glucose are measured on the automated analyzer, Integra 400 plus (Roche Diagnostics, Indianapolis, IN). All reagents, calibrators and controls are purchased from Roche. LDL is measured directly in serum or plasma with an enzymatic colorimetric assay. Alternatively, LDL can be calculated from total cholesterol, HDL and triglyceride values using the Friedewald formula: LDL= Tot Cho-HDL-Trig(0.2) (in mg/dL).26 HbA1c is calculated from two measurements in whole blood, total hemoglobin (HB-W2) and glycated hemoglobin (A1-W2), using a turbidimetric inhibition immunoassay. The ratio of glycated to total hemoglobin is calculated by the instrument, using the formula (A1-W2/HB-W2) X 91.5 +2.15, according to DCCT/NGSP.27 CRP is measured is serum or plasma using a high sensitivity, particle enhanced turbidimetric assay. Glucose is measured in plasma with NaF preservative using an enzymatic reference method.28

**Recruitment and Feasibility:**

**Estimate of Sample Size:** 836 patients

**Recruitment:** Once approved by the NCI Central Institutional Review Board, the protocol and consent will be made available to NCORP sites on the SWOG website and the Clinical Trials Support Unit (CTSU) website. Participants will be recruited from NCORP sites and screened for the following eligibility criteria (see page 3).

**Feasibility and Expected Accrual:**The anticipated accrual rate is based on SWOG 1105, which after accounting for 3 months of IRB approval and study ramp-up time, enrolled 45 patients per month. Accrual to this study is expected to be slightly slower, based on differences in study population (in particular, the cardiac risk factors). For design purposes, we assume a rate of 35 patients per month to complete enrollment in 2 years, including IRB approval and study ramp-up time.

**Multi-site SWOG study coordination:** Our proposed study will leverage the resources of the NCI Community Oncology Research Program (NCORP).29 NCORP is a nationwide network of sites that includes a diverse group of institutions and physicians including academic centers and community practice oncologists. The goal of NCORP is to offer multi-site trials, including cancer care delivery research studies and cancer survivorship studies to individuals in their own communities.30 The Group’s current network includes more than 4,000 physicians, who practice at 650 institutions across the U.S. From 2007 through 2012, SWOG investigators published more than 600 articles and abstracts, and enrolled more than 20,000 patients into trials. A total of 6,710 patients have entered on cancer prevention and control trials. Since its inception in 1956, the Group has accrued more than 200,000 patients onto clinical studies.

The NCORP structure consists of community sites, minority/underserved (MU) community sites, and research bases. Our trial will be undertaken through the SWOG NCORP research base. An important strength of the NCORP structure is the diversity of sites for participation that represent a variety of practice settings, demographic and payer mix diversity, and unique incentive structures. As such, the findings of these studies will be generalizable to oncology practice, not just at highly selected tertiary centers.

|  |  |
| --- | --- |
| **Table 2. Schedule of Procedures** |  |
| **MEASURE** | **Screening** | **Baseline** | **24 weeks** | **52 weeks** | **104 weeks** |
| *Pre-Enrollment:* |  |  |  |  |  |
|  Eligibility criteria | X |  |  |  |  |
|  Registration | X |  |  |  |  |
| *Clinical measures:* |  |  |  |  |  |
| Medication checklist |  | X | X | X | X |
| Blood pressure |  | X | X | X | X |
| Anthropometric measures |  | X | X | X | X |
| Fasting blood draw |  | X | X | X | X |
| FR-10 |  | X | X | X | X |
| Life’s Simple Seven |  | X | X | X | X |
| *PROs:* |  |  |  |  |  |
|  Demographics |  | X |  |  |  |
|  IPAQ |  | X | X | X | X |
|  PROMIS 29 |  | X | X | X | X |
|  TSQM/Adherence |  | X | X | X | X |
| *Intervention:* |  |  |  |  |  |
| Text Intervention |  | 4 x a week | 1 x a week |  |
| Control |  |  |  |  |  |

**Strengths and Weaknesses**

1. Our study design of a randomized controlled trial is scientifically **rigorous** with broad inclusion criteria, randomization, common outcomes and meaningful endpoints. The results will be generalizable due to the use of the NCORP system involving diverse practices throughout the U.S.
2. The specifics of all components of the protocol will be made available to other researchers, and data will be made available for **reproducibility** by the NCI data use standard agreements.
3. This study could establish a feasible low-cost strategy to improve cardiovascular health and medication adherence, which have a known impact on survival.
4. The use of a large NCI cooperative group in which to recruit the study population and conduct the trial brings to bear a large effective infrastructure designed for the efficient and successful conduct of trials with intensive oversight and heavy investment of resources that will be leveraged by this grant.
5. The diverse patient population recruited from both academic centers, minority institutions and community oncology clinics throughout the U.S. will enhance the generalizability of the findings.
6. The key investigators represent an experienced multidisciplinary group with extensive experience in the key areas necessary for the success of this study, including the successful conduct of trials within the cooperative group setting, and have studied breast cancer treatment adherence for several years.
7. The study will use a one-way text as opposed to a bi-directional text intervention. Two-way communication requires additional resources: monitoring of the “send-receive” loop, tracking of the conversation (to see which message is linked with which response), personnel to oversee and respond to messages, and the economic cost of replies via text message which must be either borne by the participant or charged back to the study.
8. A potential weakness is that the short-term intervention will not have lasting effects, however, we will get information on the durability of the intervention with a maintenance phase and will evaluate if any effects persist following discontinuation of the intervention.
9. A limitation is that change in LDL-C at 24 weeks is a short-term surrogate endpoint that may correlate with long-term cardiovascular events. The TEXT-ME trial found an improvement in other cardiac risk factors (systolic blood pressure, weight, smoking, and physical activity), which may not only improve cardiovascular outcomes but also may improve breast cancer outcomes.
10. Another potential limitation is that patients will need to sign a consent and will be aware to some degree of the conduct of the study and its purpose and this may influence their behavior, *i.e.*, a Hawthorne effect. This could affect, for example, medication adherence or response on patient reported outcomes. However, our primary endpoint, LDL-C, is an objective measure, which is not subject to this bias.

**Statistical Plan and Analysis:**

|  |
| --- |
| **Table 4.** Power calculations |
| Dropout | Non-adherence |
| 5% | 7.5% | 10% | 12.5% | 15% |
| 10% | 90% | 88% | 86% | 84% | 82% |
| 12.5% | 89% | 87% | 85% | 83% | 81% |
| 15% | 88% | 86% | 84% | 82% | 79% |

Primary Endpoint

|  |
| --- |
| **Table 5: Power to detect a specified difference in outcome**  |
| Normal DesignRatio of Standard Deviation to Detected Difference |
|  | 5:1 | 4.5:1 | 4:1 | 3.5:1 | 3:1 |
| Power | 80% | 88% | 94% | 98% | >99% |
| Binomial design Absolute difference between arms (overall event rate is 50%) |
|  | 10% | 11% | 12% | 13% | 14% |
| Power | 79% | 86% | 91% | 95% | 97% |

The primary endpoint for this study is serum LDL-C at 24 weeks after randomization. LDL-C was chosen for a number of reasons. First, it was the primary endpoint of the TEXT-ME intervention that serves as the basis for this study. Second, based on a meta-analysis from 90,000 patients, the relationship between decrease in LDL-C and reduction in cardiovascular risk has been established such that a 10 mg/dl reduction (same endpoint as TEXT-ME) translates to a 6% reduction in major cardiovascular events.31 This sample size will also allow for the evaluation of multiple secondary endpoints including systolic blood pressure, physical activity, and BMI.

Two stratification factors representing patient cardiovascular risk will be obtained at baseline: the baseline fasting LDL-C (<130 vs ≥130) and the Framingham 10-year CVD risk (<10% vs. ≥10%).32 Patient randomization will be dynamically balanced by using the method of Pocock & Simon.33 The primary assessment time of 24 weeks, upon which power calculations are based, corresponds to completion of the intervention at the rate of 4 text messages administered per week.

This study stipulates an alpha=.05 two-sided test, with an estimated 5% intervention non-adherence (reducing the nominal effect size) and 10% dropout rate (increasing the total required sample size) at 24 weeks after randomization. In addition, the design will incorporate a 10% contamination rate (which also reduces the nominal effect size) to account for the likelihood that some patients on the control arm may adopt behavioral changes to reduce their cardiovascular risk, due to the fact they recognize they are on a study about reducing cardiovascular risk (the “Hawthorne” effect). This population of patients is assumed to have no benefit from intervention.

The study design targets a difference in LDL-C of 10mg/dl at 24 weeks after randomization between the control and intervention groups. Data from prior studies indicate that the standard deviation for LDL-C at 6 months in similar settings was about 35 mg/dl, common to both standard and intervention arms.14,34 Based on these parameters and assuming a 2-sided alpha=.05 test of the intervention effect at on LDL-C at 24 weeks, 794 patients would be required for 90% power using a two arm normal design. To account for an expected 5% ineligibility rate, n=836 total patients will be required. The primary endpoint will be assessed using multivariable linear regression, adjusting for the single stratification factor and the baseline LDL-C value.

Secondary Endpoints

Assessment of 52 and 104 week outcomes, including the potential long-term and mitigating effects of maintenance text messaging on differences by intervention arm, will also be conducted as secondary analyses. For these longer-term assessments, we anticipate higher non-adherence and dropout, although the contamination rate is expected to remain the same. For the specified sample size to detect a difference of 10mg/dl, power will vary as a function of the non-adherence and dropout levels as shown in Table 4 above. A longitudinal analysis incorporating all serial assessments (24, 52, and 104 weeks) will also be conducted, using linear mixed models with subject specified as a random effect. The mixed model analysis will test time as linear and quadratic covariates, along with intervention effect, their interaction (to assess potentially differing trajectories of LDL-C over time by arm), the baseline score, and the stratification factors.

Additional secondary objectives include assessment of the relationship between randomized arm and systolic blood pressure, BMI, physical activity, and smoking status at 24 weeks. Reflecting the different analytic approaches required for each outcome type – that is, linear (i.e. systolic blood pressure) vs. logistic (i.e. smoking status) regression – representative power estimates are based on two arm normal and two arm binomial designs (respectively), with two-side alpha=.05 and 794 eligible patients. The estimates shown in Table 5 indicate how power to detect a specified difference in an outcome will vary by the ratio of standard deviation to detected difference for two-arm normal designs and absolute difference between arms for two-arm binomial designs. Analyses will be conducted using linear or logistic regression, as appropriate, adjusting for stratification factors and the baseline value. All secondary endpoint analyses will be considered hypothesis generating, requiring confirmation under independent study.

**Cost-Effectiveness Analysis:** We will do an exploratory analysis to model the cost-effectiveness of the text messaging intervention vs. usual care from the health care perspective under the assumption that the health care system would incur the costs of maintaining the reminder message system. This perspective has the advantage of providing relevant stakeholders with upfront and downstream costs and benefits, and may be useful for justifying the investment decision, should the technology prove effective. Relevant costs include the costs of the text messaging intervention itself, costs of cardiovascular events and the costs of recurrent breast cancer, risks of recurrent breast cancer related to non-adherence. Benefits will be determined by the reduction in each of the cardiovascular risk factors and improvement in adherence. Cardiovascular events and estimated risk of dying from breast cancer will be modeled from the literature

To estimate cost effectiveness, the difference in the arithmetic mean total cost will be compared using a generalized linear model. Incremental differences in cost and effectiveness will be used to calculate an Incremental Cost-Effectiveness Ratio (ICER)—*i.e.,* the additional cost per reduction of estimated CVD events. Uncertainty analysis will be evaluated using one-way sensitivity analysis and multi-way probabilistic analysis and construction of acceptability curves using non-parametric bootstrapping.35

**Research’s Impact** To our knowledge, this will be the first large-scale intervention trial to investigate a feasible, cost-effective strategy for improving cardiovascular outcomes in breast cancer survivors, an extremely common problem with serious ramifications for overall survival. Text messaging is now widely available and inexpensive and therefore, if successful, it will be easily translatable into clinical use by pharmaceutical companies or insurance companies or other large-scale providers. From a cost effectiveness perspective, it is likely to be very effective in reducing cardiovascular events and recurrence/mortality from breast cancer (due to improved drug adherence and reduced CVD/breast cancer risk factors), with the accompanying reductions in financial costs. One of the reasons we have opted to intervene on CVD risk among breast cancer survivors with text messaging is that it lends itself easily to early adoption in the real world if it proves efficacious.

**References:**

 1. Cancer facts and figures 2010. Atlanta, GA, American Cancer Society, 2010

 2. DeSantis CE, Lin CC, Mariotto AB, et al: Cancer treatment and survivorship statistics, 2014. CA Cancer J Clin 64:252-71, 2014

 3. Heidenreich PA, Trogdon JG, Khavjou OA, et al: Forecasting the future of cardiovascular disease in the United States: a policy statement from the American Heart Association. Circulation 123:933-44, 2011

 4. Yusuf S, Hawken S, Ounpuu S, et al: Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet 364:937-52, 2004

 5. Schairer C, Mink PJ, Carroll L, et al: Probabilities of death from breast cancer and other causes among female breast cancer patients. J Natl Cancer Inst 96:1311-21, 2004

 6. Patnaik JL, Byers T, DiGuiseppi C, et al: Cardiovascular disease competes with breast cancer as the leading cause of death for older females diagnosed with breast cancer: a retrospective cohort study. Breast Cancer Res 13:R64, 2011

 7. Bradshaw PT, Stevens J, Khankari N, et al: Cardiovascular Disease Mortality Among Breast Cancer Survivors. Epidemiology 27:6-13, 2016

 8. Accordino MK, Neugut AI, Hershman DL: Cardiac effects of anticancer therapy in the elderly. J Clin Oncol 32:2654-61, 2014

 9. Johnson CB, Sulpher J, Stadnick E: Evaluation, prevention and management of cancer therapy-induced cardiotoxicity: a contemporary approach for clinicians. Curr Opin Cardiol, 2015

 10. Shelburne N, Adhikari B, Brell J, et al: Cancer treatment-related cardiotoxicity: current state of knowledge and future research priorities. J Natl Cancer Inst 106, 2014

 11. Darby SC, Ewertz M, McGale P, et al: Risk of ischemic heart disease in women after radiotherapy for breast cancer. N Engl J Med 368:987-98, 2013

 12. Hershman DL, Neugut AI: Anthracycline cardiotoxicity: one size does not fit all! J Natl Cancer Inst 100:1046-7, 2008

 13. Thakkar J, Kurup R, Laba TL, et al: Mobile Telephone Text Messaging for Medication Adherence in Chronic Disease: A Meta-analysis. JAMA Intern Med 176:340-9, 2016

 14. Chow CK, Redfern J, Hillis GS, et al: Effect of Lifestyle-Focused Text Messaging on Risk Factor Modification in Patients With Coronary Heart Disease: A Randomized Clinical Trial. JAMA 314:1255-63, 2015

 15. Chow CK, Redfern J, Thiagalingam A, et al: Design and rationale of the tobacco, exercise and diet messages (TEXT ME) trial of a text message-based intervention for ongoing prevention of cardiovascular disease in people with coronary disease: a randomised controlled trial protocol. BMJ Open 2:e000606, 2012

 16. Cutter GR, Burke GL, Dyer AR, et al: Cardiovascular risk factors in young adults. The CARDIA baseline monograph. Control Clin Trials 12:1S-77S, 1991

 17. Gehi A, Haas D, Pipkin S, et al: Depression and medication adherence in outpatients with coronary heart disease: findings from the Heart and Soul Study. Arch Intern Med 165:2508-13, 2005

 18. Morisky DE, Green LW, Levine DM: Concurrent and predictive validity of a self-reported measure of medication adherence. Med Care 24:67-74, 1986

 19. Ghali JK, Kadakia S, Cooper R, et al: Precipitating factors leading to decompensation of heart failure. Traits among urban blacks. Arch Intern Med 148:2013-6, 1988

 20. Godin G, Gagne C, Naccache H: Validation of a self-reported questionnaire assessing adherence to antiretroviral medication. AIDS Patient Care STDS 17:325-32, 2003

 21. Bharmal M, Payne K, Atkinson MJ, et al: Validation of an abbreviated Treatment Satisfaction Questionnaire for Medication (TSQM-9) among patients on antihypertensive medications. Health Qual Life Outcomes 7:36, 2009

 22. Craig CL, Marshall AL, Sjostrom M, et al: International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exerc 35:1381-95, 2003

 23. D'Agostino RB, Sr., Grundy S, Sullivan LM, et al: Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. JAMA 286:180-7, 2001

 24. Lloyd-Jones DM, Hong Y, Labarthe D, et al: Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic Impact Goal through 2020 and beyond. Circulation 121:586-613, 2010

 25. Gibbs BB, King WC, Belle SH, et al: Six-month changes in ideal cardiovascular health vs. Framingham 10-year coronary heart disease risk among young adults enrolled in a weight loss intervention. Prev Med 86:123-9, 2016

 26. Friedewald WT, Levy RI, Fredrickson DS: Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 18:499-502, 1972

 27. Hoelzel W, Weykamp C, Jeppsson JO, et al: IFCC reference system for measurement of hemoglobin A1c in human blood and the national standardization schemes in the United States, Japan, and Sweden: a method-comparison study. Clin Chem 50:166-74, 2004

 28. Vaccaro O, Masulli M, Cuomo V, et al: Comparative evaluation of simple indices of insulin resistance. Metabolism 53:1522-6, 2004

 29. NCI Community Oncology Research Program (NCORP).

 30. NCORP Research Areas.,

 31. Baigent C, Keech A, Kearney PM, et al: Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet 366:1267-78, 2005

 32. Wilson PW, D'Agostino RB, Levy D, et al: Prediction of coronary heart disease using risk factor categories. Circulation 97:1837-47, 1998

 33. Pocock SJ, Simon R: Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. Biometrics 31:103-15, 1975

 34. Vale MJ, Jelinek MV, Best JD, et al: Coaching patients On Achieving Cardiovascular Health (COACH): a multicenter randomized trial in patients with coronary heart disease. Arch Intern Med 163:2775-83, 2003

 35. Briggs AH, O'Brien BJ, Blackhouse G: Thinking outside the box: recent advances in the analysis and presentation of uncertainty in cost-effectiveness studies. Annu Rev Public Health 23:377-401, 2002

1. The NSC Number must be provided if the agent is investigational. See <http://ctep.cancer.gov/protocolDevelopment/codes_values.htm#agent> for a complete list of Organization (Group, Consortium and Institution), IND and NSC Numbers and Disease Names and Codes. [↑](#footnote-ref-1)