cardiovaScUlar toxicity in canceR and improVement In recoVEry Registry

SURVIVE Registry

Study Protocol v1.0

January 25, 2018

PRINCIPAL INVESTIGATOR

Daniel J. Lenihan, MD
Professor of Medicine
Washington University School of Medicine
Division of Cardiology
660 South Euclid Ave, Campus Box 8086
St. Louis, MO 63110
Email: djlenihan.@wustl.edu

WASHINGTON UNIVERSITY CO-INVESTIGATORS

Division of Cardiology

Ronald Krone, MD
Professor of Medicine

Joshua Mitchell, MD
Cardiology Fellow

Holly Wiesehan, MSN, AGACNP
Cardio-Oncology Nurse Practitioner

John Gorcsan III, MD
Professor of Medicine
SURVIVE Imaging Core Lab Director

Kaitlin Moore, BS
Clinical Research Coordinator
SURVIVE Biobanking Core Lab Director

Eric Novak, MS
Biostatician

Division of Medical Oncology

Keith Stockerl-Goldstein, MD
Associate Professor of Medicine

Neha Mehta-Shah, MD
Associate Professor of Medicine

Lindsay Peterson, MD, MSCR
Assistant Professor of Medicine

Nancy Bartlett, MD
Professor of Medicine

Division of General Medical Sciences

Randi Foraker, PhD, MA, FAHA
Associate Professor of Medicine

COORDINATING CENTER

Washington University St. Louis

POTENTIAL PARTICIPATING SITES

Brigham & Women's Hospital
Franciscan St. Francis Health
Stanford University Medical Center
University of Kansas Medical Center
University of South Florida Health
Vanderbilt University School of Medicine
Duke University
The Mayo Clinic
University of British Columbia
University of Pennsylvania
University of Texas Southwestern
MedStar Health

TABLE OF CONTENTS

1.0 BACKGROUND

There is an impressive increase in cancer survivors over the past decade and current estimates report there are more than 14 million cancer survivors in the U.S. with an expectation to continue expanding this population largely due to the success of cancer therapy. A major issue that is now quite apparent in cancer survivors is that cardiovascular disease (CVD) contributes greatly to the increased morbidity and early mortality in patients treated for cancer when compared to age-matched patients without cancer [1,2]. Furthermore, active cancer therapy, either chemotherapeutics or radiation, is increasingly being recognized as having important cardiovascular toxicity (CVTx) that may limit optimal cancer treatment. Classically, cardiotoxicity was specifically defined by left ventricular systolic dysfunction, as documented by a reduction in left ventricular ejection fraction (LVEF), and in the context of anthracycline based chemotherapy administration. The current and future era of cancer therapeutics is infinitely more complex and targeted than just the use of anthracyclines. It is imperative that medical providers recognize that the potential CVTx that may occur during cancer therapy in the present day cannot be simply defined by a method that was initiated 40 years ago. Similarly, the initial observations regarding cardiac dysfunction related to anthracyclines indicated that cardiac damage was frequently permanent. Recent data, focusing on early detection and treatment of anthracycline cardiac dysfunction, reveals that this problem is commonly reversible, at least in part, if effective treatment is promptly initiated [3,4]. Given that there are many cancer therapeutics that have uniquely targeted mechanisms and equally as many that are associated with CVTx [5,6], it is abundantly clear that understanding and identifying potential CVTx is a mandate [7]. Moreover, defining effective CV treatments that can minimize any CV impact for a patient being treated for cancer and allowing recovery of a CV injury is a major clinical need [8,9].

2.0 RATIONALE AND SPECIFIC AIMS

The **rationale** of this registry is based upon the following:

In order to understand the CV impact of contemporary cancer therapy, carefully done clinical research must be undertaken to clarify the mechanisms of CVTx, recognize the typical presentation and discern the best methods for clinical detection, describe optimal therapeutic options as well as identify potential strategies for prevention of cardiovascular dysfunction. The SURVIVE Registry is a proposal to meet these important goals.

The specific aims for the SURVIVE Registry are:

1) Identify the cancer therapeutics and the cancer conditions in which cardiovascular dysfunction, potentially as a result of cancer therapy, can recover back to pre-chemotherapy levels or improve substantially with effective cardiac treatment.

The majority of adult CVTx that has been reported is in patients with breast cancer; however, there are certainly higher risk populations for the development of cardiac complications. It is clear that the knowledge base that has been formed is because breast cancer is very common but also the initial cancer therapies were connected to

CVTx. Other cancer disease states may have significant CV risks; however, completely different targeted cancer therapy is typically used. As a result, little is known about the significance and potential reversibility of CVTx in other cancer conditions. In the case of breast cancer, there is a strong suggestion that early detection and effective treatment of cardiac dysfunction may allow continued trastuzumab therapy [10,11], but is not always the final outcome [12]. Especially when anthracyclines are used in the treatment of breast cancer, the improvement back to normal or pre-chemotherapy baseline is frequently incomplete. In the situation that has been observed in patients with renal cell cancer who are treated with altogether different treatments, patients receiving anti-vascular endothelial growth factor (VEGF) therapy may develop severe hypertension and subsequently cardiac dysfunction, there is a suggestion that cardiac dysfunction may be reversible [13], but this is by no means established consistently [14,15]. For example, patients with multiple myeloma who are treated with combination chemotherapy over a relatively long period of time, it is not established at all what mechanisms may be responsible for a high incidence of heart failure and cardiac dysfunction in patients with multiple myeloma seen in recent major trials [16,17]. At least one suspected mechanism responsible is the irreversible binding of the proteasome by carfizomib while the potential recovery of cardiac dysfunction is not established [18]. These examples illustrate that as newer targeted therapy is developed in a host of cancer conditions, it is consistently being discovered that CV tissue may be susceptible to targeted inhibition. Not only is there an unknown level of risk for CVTx with newer therapies, the recovery or likelihood of recovery of cardiac function is completely unknown. In the current paradigm of developing targeted therapy for a host of cancer populations each with peculiar demographic characteristics, careful clinical observation and combined synchronized data reporting is essential.

2) Describe the clinical tools that are most useful and cost effective at promoting recovery of cardiovascular dysfunction.

Ultimately, the goal in cardio-oncology evaluation is to identify patients at highest risk before chemotherapy to allow for modification of that risk, identify cardiotoxicity as early as possible in an attempt to prevent significant LV dysfunction, and to maximize recovery of function for those patients who do suffer from LV dysfunction. For all three of these goals, the current evidence is limited or lacking and the SURVIVE database will allow us learn and understand what may be the most effective strategies.

Numerous risk factors have been identified that have been associated with increased CV risk from chemotherapy including standard CV risk factors (older age, smoking, hypertension, hyperlipidemia, diabetes) as well as chemotherapy regimens (doxorubicin >= 250 mg/m2, epirubicin >= 600 mg/m2, radiation >= 30 Gray)[19]. There is limited research, however, that comprehensively evaluates these risk factors in determining the patient's overall risk. In addition, only one risk prediction score has been computed for older patients with breast cancer receiving trastuzumab[20], and this model has not been validated in other cancer populations.

For prevention of cardiotoxicity in patients at risk, several small studies have evaluated treatment with beta-blockers or inhibitors of the renin-angiotensin-aldosterone system. There is some evidence for the use of selected beta-blockers, ACE-I, or ARB, to prevent cardiomyopathy in high risk patients, but these studies have been in smaller populations (typically less than 130 patients) and the results of these studies have potentially

conflicting results depending on the intensity of cancer treatment or the co-morbidity that may exist with each study[21-23].

Once LV dysfunction has been identified, there is some evidence that early treatment with cardio-protective medication improves the chances of recovery[24]. There is a strong impetus, therefore, to identify methods that are most sensitive and specific for early signs of cardiotoxicity. Small studies have identified some potentially useful novel echocardiography imaging techniques, such as s strain or strain rate, in addition to surveillance with cardiac biomarkers such as troponin or natriuretic peptides[25,26]. An example of this strategy demonstrated that treating patients (total n=114) with positive troponin after chemotherapy with enalapril helped prevent late cardiac toxicity[27].

Overall, the evidence in cardio-oncology remains optimistic but realistically limited to guide the cardiology and oncology teams in the optimal methods to improve long-term cardiac health in patients undergoing cancer treatment. To that end, we will perform a comprehensive baseline risk factor assessment in order to determine the best risk prediction models for patients undergoing cancer therapy. One recently developed proprietary tool that augments the AHA ASCVD prediction tool with additional cancer risk models will be evaluated prospectively for its ability to predict outcomes in SURVIVE patients. We will also evaluate the impact that use of the tool has on practice patterns after integration into the electronic health record. Furthermore, a comprehensive clinically driven sophisticated imaging and biomarker evaluation of patients will be done to identify what tools and which results are key drivers for the optimal early identification of cardiotoxicity. Finally, we will analyze the impact of cardioprotective medications in preventing and aiding the recovery from LV dysfunction.

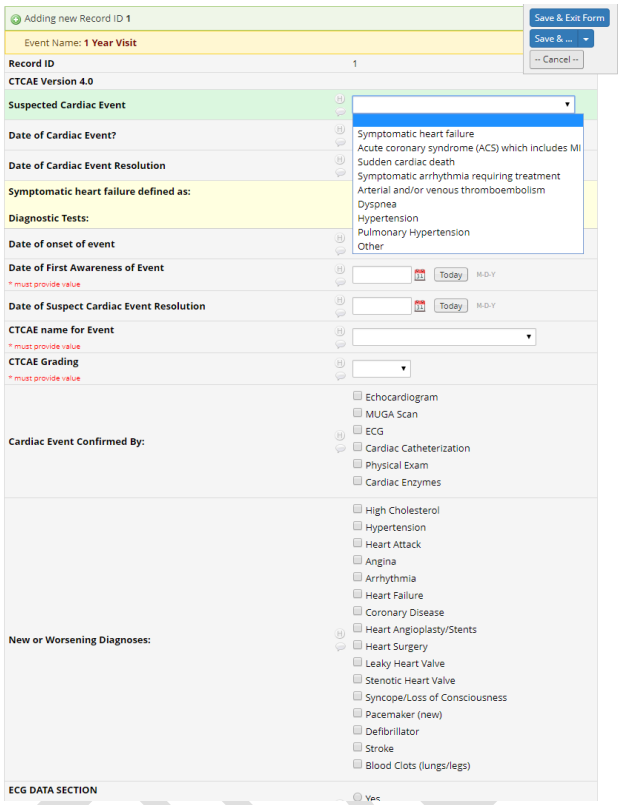
3) Improve the clinical detection, treatment, and outcomes of patients with cardiovascular dysfunction that occurs during or as a result of cancer therapy.

In order to establish what techniques are best to utilize to improve outcomes of patients with cancer who have cardiovascular disease, it is necessary to identify those who have cardiovascular disease at baseline and those who develop cardiovascular disease during treatment. As such, we will enroll patients with a history of cancer who have cardiovascular disease prior to, during, or after cancer treatment.

Data Collection Instrument	Baseline Visit	6 Month Visit	1 Year Visit	2 Year Visit	3 Year Visit	Phone Follow Up
Inclusion/Exclusion Criteria Checklist	●					
Enrollment Form Basic Info	●					
Physical Exam And Vitals	●	●	●	●	●	
Medical History	●	●	●	●	●	
Cardiac, Oncology, and Other Meds	●	●	●	●	●	●
Laboratory Values	●		●	●	●	
Blood Sample Collection ID's	●	●	●	●	●	
Echo Data	●		●	●	●	
ECG	●		●	●	●	
MRI	●		●	●	●	
Cardiac Catheterization	●		●	●	●	
Stress/Exercise Testing	●		●	●	●	
Six-Minute Walk Test	●	●	●	●	●	
Health Status Questionnaires	●		●	●	●	
Sensitive Information Questionnaire	●					
Cardiovascular Risk Assessment Questionnaire	●	●	●	●	●	
Cardiovascular Risk Factors	●	●	●	●	●	
Past And Present Cancer History	●		●	●	●	
Chemotherapy Treatment 1	●	●	●	●	●	
Chemotherapy Treatment 2	●	●	●	●	●	
Chemotherapy Treatment 3	●	●	●	●	●	
Chemotherapy Treatment 4	●	●	●	●	●	
Chemotherapy Treatment 5	●	●	●	●	●	
Suspected Cardiac Event	●	●	●	●	●	●
Phone Interview Questionaire						●
Outcomes			●	●	●	
Follow Up Survival Status			●	●	●	
Notes To File	●	●	●	●	●	●
Study Exit Form	●	●	●	●	●	●

Methods: All adult patients (≥18 years old) with any evidence of cardiovascular dysfunction documented by history, physical, laboratory or imaging methods in a patient who has been previously treated or currently receiving active treatment for cancer. All patients will provide informed consent. A host of clinical factors will be documented and baseline serum, plasma, and cells for DNA will be banked and processed for each patient. There

will be repeat testing determined by clinical care at least at intervals of 6 months, 1, 2, and 3 years after enrollment, with additional visits tabulated for any suspected cardiac event.



3.0 INCLUSION AND EXCLUSION CRITERIA

A. Inclusion Criteria

- All adult patients (≥ 18 years old) at time of consent
- Previously treated or has planned treatment for any type of cancer at any stage
- Evidence of cardiovascular dysfunction or presence of at least one cardiovascular risk factor documented by history, physical, laboratory, or imaging methods

B. Exclusion Criteria

- Inability or refusal to provide informed consent (Legally Authorized Representatives (LARs) are permitted)

4.0 ENROLLMENT

There will be various ways a patient can enroll in the SURVIVE Registry either at the Cardiovascular-Oncology Coordinating Center or at a Participating Site. These are as follows:

1. Research personnel, including study physicians, will identify possible registry candidates composed of inpatient and outpatient clinic settings. If patients

appear to be potential study candidates, research personnel will discuss the study with these patients during their outpatient clinic visit or hospital stay. Interested patients who qualify for the study will be consented at this time.

2. Interested patients will be encouraged to ask their physicians about the registry. If patients appear to be potential study candidates and they wish to learn more about taking part in the registry, research personnel will be contacted to speak to them about the study. Interested patients who qualify for the study will be consented at this time.

During the consenting process, the candidate will receive an IRB approved consent form to read and any questions the candidate has will be answered by the research staff. Candidates who do not agree to enroll will continue with their standard care and their decision not to participate will not interfere. If they wish to take part in the study, they will sign the IRB approved consent form. Each candidate will receive a copy of the signed IRB approved consent form.

After the patient has been consented at the Cardiovascular-Oncology Coordinating Center or a Participating Site, they will be entered into the REDCap database within 5 business days of the visit.

5.0 STUDY PROCEDURES

A subject's length of time in this study will be indefinite, unless they withdraw consent.

A. Study Visits

i. Schedule of Events

	Baseline Visit	6 Months after Baseline Visit	Yearly Visit
Informed Consent	X		
Inclusion/Exclusion Criteria	X		
Medical/Clinical History	X	X	X
Imaging Data	X	X	X
Laboratory Data	X	X	X
Medications	X	X	X
Vital Signs	X	X	X
Cardiovascular Health Score	X	X	X
Blood Collection	X	X	X
Other Specimen Collection	X	X	X
Sensitive Information Questionnaire	X		
EQ-5D Questionnaire	X	X	X
Cardiovascular Risk Assessment Questionnaire	X	X	X

ii. Initial Baseline Visit

After the subjects have given consent and enrolled in the registry, approximately 2 to 3 tablespoons of blood will be drawn from subjects during their hospital stay or out-patient visit. Every effort will be made to draw blood for this registry at the same time blood is being drawn for standard care.

Other biological samples that may be collected are left over clinical specimens of cardiovascular or cardiovascular disease-related tissue. No tissue will be collected specifically for this registry. Additional biological samples include urine samples as well as saliva samples.

All data will be collected at the bedside, by phone, by mail on paper or via electronic forms with review of medical record. Data will then be entered into a REDCap database either by electronic transfer or directly by the research personnel using the subject's unique study number. The subjects may be contacted through email to answer surveys. The subject's study number will serve to identify them in the database.

The subject will be asked to complete the Sensitive Information Questionnaire (Appendix A), the EuroQol 5D-5L (EQ-5D) Questionnaire (Appendix B) and the Cardiovascular Risk Assessment Questionnaire (Appendix C) at the Baseline Visit. These questionnaires will take about 10 minutes to complete. If any of the questions in the Sensitive Information Questionnaire, EQ-5D Questionnaire, or Cardiovascular Risk Assessment Questionnaire makes the participant feel uncomfortable and they do not want to answer these questions at any time they can mark that they prefer not to answer. These questionnaires will not contain any identifying information. Each questionnaire will be labeled with the subject's study ID.

Participants' medical records will be reviewed and requested data – such as past medical history, vital signs, laboratory data, medications, Cardiovascular Health Score, etc. – entered into REDCap.

iii. *Follow Up Visits*

Six months after the baseline visit and then each year, all subjects will be screened for upcoming clinical visits. Patients with upcoming appointments will be approached for their annual follow-up in any clinical setting. If patients are admitted to the hospital around the time that they are due for follow-up, they may be approached as an inpatient by the registry personnel to complete the follow-up. Registry patients without upcoming appointments will be contacted by phone, mail, and/or email.

At the time of follow-up, the subjects will be asked to complete the EuroQol 5D-5L Questionnaire (Appendix B) and the Cardiovascular Risk Assessment Questionnaire (Appendix C). Completing this follow-up questionnaire should take approximately 5 minutes. Any questionnaires mailed to the subject will include a self-addressed stamped envelope for the subject to mail back the questionnaires, as well as the research personnel's contact information if the subject needs any assistance completing the questionnaires. Patients who do not return the follow-up materials in a timely manner will be contacted via phone by a member of the registry staff.

All subjects with upcoming appointments may be asked for another urine sample and blood sample (approximately 2 to 3 tablespoons total) at any standard of care (SOC) visit. The blood and/or urine may be used for future clinically relevant research studies such as biomarker development, circulating hormone levels, genetic testing, or other undefined studies. Donation of biological samples is optional.

For subsequent visits, participants' medical records will be reviewed and requested data – such as vital signs, laboratory data, medications, Cardiovascular Health Score, etc. – entered into REDCap.

B. Blood Sample Collection

Blood will be drawn by qualified nursing and/or medical staff at the Cardiovascular-Oncology Coordinating Center and Participating Sites using standard techniques and transported for processing and storage. Samples will be labeled using bar codes, which will prevent the attachment of patient identifiers to the samples. The specific blood collection, processing, and storage procedures are outlined in the SURVIVE Registry Manual of Operating Procedures. One sample may be retained for each subject at each participating site, if they choose. Otherwise, all samples will be sent to the Cardiovascular-Oncology Coordinating Center. Samples sent to the Cardiovascular-Oncology Coordinating Center will be shipped to Washington University in St. Louis where they will be logged and stored until time of analysis.

The blood will be used for clinical studies of the prognostic importance of elevated levels of specific circulating hormones (such as endothelin), studies of specific genetic polymorphisms for genotypes (such as adenosine deaminase and angiotensin converting enzyme inhibitor), biomarker development, or future undefined studies. Blood samples will not be used for patient care or other studies other than studies subsequently approved by SURVIVE Supervisory Committee and the IRB.

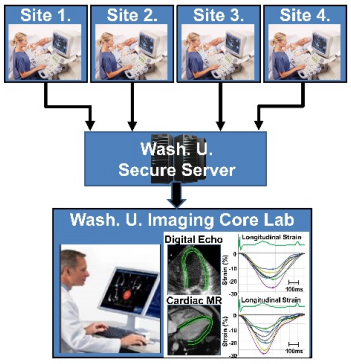
C. Imaging

Imaging will also be collected from the various study time points indicated above. All CT, echo, MRI, and other available diagnostic imaging will be uploaded de-identified from Participating Sites and reviewed by the SURVIVE Imaging Core Lab.

The proposal is for multiple sites to have a common depository at Washington University in St. Louis of digital imaging, including echocardiographic and cardiac magnetic resonance (CMR) images for cardio-oncology research purposes. The SURVIVE Imaging Core Lab director, John Gorcsan III, MD has extensive experience with receiving and handling digital echocardiographic images for multicenter clinical trials and multicenter registries. Most notable is the recent 21 site multicenter **REVIVAL Registry** Evaluation of Vital Information for VADs in Ambulatory Life (Sponsored by NHLBI) including 400 heart failure patients for left ventricular assist device (LVAD) implantation. Also, Dr. Gorcsan directed the echo core lab for several randomized clinical trials, including the 115 site multicenter international study **EchoCRT:** (Sponsor, Biotronik) with 809 patients randomized and the 94 site multicenter international study **aCRT** (Sponsor, Medtronic) with 522 patients randomized world-wide, the 26 sites multicenter study **BENEFIT:** (Sponsor, St. Jude Medical) 279 patients enrolled, and the 30 sites multicenter study **RISK:** (Sponsor, St, Jude Medical) with 267 patients enrolled. Each of

these studies involved training of sites, handling transfer of digital images, quantitative analysis and archiving.

SURVIVE Imaging Core Lab Director, John Gorcsan, MD has been recently recruited to Washington University in St. Louis as Director of Clinical Research for the Division of Cardiology and to direct the Research Echo Core Lab. The institution has provided the state-of-the-art infrastructure for upload of digital DICOM echocardiographic and CMR images to a central core lab server, which has high-level encrypted security, and is fully HIPAA compliant. Sites will be able to transmit digital echo, CMR images, and other relevant DICOM images in a user-friendly manner using any computer with an internet connection. Furthermore, an upload of an entire study is possible in approximately 1-2 minutes with average WiFi transmission speeds. No specialized hardware or software will be required by the sites. The imaging core lab has software capable of de-identifying patient data to be compliant with all IRB policies. The Research Echo Core Lab has vendor-neutral software (TomTec, Munich Germany) for quantitative analysis of DICOM echo and CMR images for routine measures, such as volumes and ejection fraction, and advanced measures, such strain imaging. The SURVIVE Imaging Core Lab will provide the instructional manual, site training, and technical assistance with all image uploads.



Multiple sites may upload digital images to user-friendly Wash U. server for download and archiving by

D. AH-HA Tool

The AH-HA Tool will be used to capture the Cardiovascular Health Score, which will be analyzed at each time point the patient returns for a clinical visit. The Cardiovascular Health Score will be developed to aid in the assessment of the patient's cardiovascular risk factor upon administration of Chemotherapy/Radiation. This tool is embedded in EPIC. The Cardiovascular-Oncology Coordinating Center will move towards using EPIC in 2018 and will work to utilize the AH-HA tool within EPIC at each visit. Participating Sites that have EPIC or are moving towards EPIC will also incorporate this tool. Participating Sites who cannot utilize this tool will collect the data points, so the Cardiovascular Health Score can still be computed.

E. Management of the Data and Repository

The bio-specimen repository will be managed by the SURVIVE BioBanking Core Lab Director and associated personnel. The SURVIVE Biobanking Core Lab Director will be responsible for managing the REDCap database where the data will be stored, as well as accessing and distributing the samples and data to the investigators. Any samples and/or data optimized for investigators will be approved by the SURVIVE Supervisory Committee and have an IRB approved study number.

F. Data Safety and Monitoring

The Principal Investigator (PI) at each site will take primary responsibility to follow enrolled participants. Only adverse events from blood draw and/or breach of confidentiality will be reported. Adverse events will be documented in the subject's research record, as well as REDCap, and reported to the IRB per institution guidelines. For more information on Adverse Events, see Section 7.0 of this protocol.

The data consist of information obtained from the study data forms, mailed/emailed questionnaires, and phone surveys. Data will be stored in two places: 1) REDCap as previously mentioned and 2) all original paper copies will be stored in a locked cabinet behind a locked door. Moreover, only the Research Coordinator or designated study staff will have keys to the locked cabinet. Only the designated study staff will have access to any resources with identifying information in REDCap. An important REDCap feature to note is that the access to study data is limited to those assigned access (i.e. Key Study Personnel [KSP]).

Monitoring will consist of data checks, both electronic and manual. Every 6 months data entered into the REDCap database will be reviewed for accuracy by designated study staff at the Cardiovascular-Oncology Coordinating Center. Uploaded source documentation will also be reviewed for inconsistent data. If there are inconsistencies or missing values, queries will be issued to the Participating Sites and they will refer to the subject's electronic record to correct the aberration. Participating sites are expected to enter data into REDCap within 14 business days of a study visit. Sites that appear to have significant delays between the time of enrollment/study visits and data entry will be contacted by the Cardiovascular-Oncology Coordinating Center. Participating sites are also expected to respond to any REDCap queries within 1 month of issuance. Sites that appear to have a significant amount of REDCap queries will be contacted by the Cardiovascular-Oncology Coordinating Center. At each interval, the Cardiovascular-Oncology Coordinating Center will note the number of participants accrued to date as well as the number of participants accrued for that 6 months interval.

The Director of the SURVIVE Biobanking Core Lab at the Cardiovascular-Oncology Coordinating Center will maintain and monitor the storage and organization of the biological samples maintained in the study freezer and this information will also be stored in REDCap. The location of the samples stored in the freezer will be verified against the location of the samples in the organizational chart.

All study personnel will receive training on protocol procedures and data collection from the Cardiovascular-Oncology Coordinating Center. Only experienced personnel will take part in this study. Additionally, designated study staff will randomly monitor the consenting process pertinent to this study to maintain study protocol compliance, as well as ensure the minimization of measurement or information bias imposed by study personnel.

6.0 RISKS AND BENEFITS

A. Risks

This study is a minimal risk study. However, the following are potential risks to the participant:

i. *Blood Draw Risks:*

The risks of blood draw include brief pain, bleeding, and possibly a small bruise at the needle site. Occasionally, a person feels faint when blood is drawn. Infections from blood draws develop rarely and can be treated. Every attempt will be made to draw blood at the same time as blood is being drawn for

medically indicated purposes, avoiding the need for an additional needle stick. If we are not able to draw blood at the same time as blood is being drawn for standard care then only qualified medical and/or nursing staff will draw the subject's blood used for this registry. Furthermore, there is a minimal risk of accidental release of confidential information.

ii. *Saliva Sample Risks:*
Each method might have an unpleasant taste. Additionally, there could be a release of their protected health information that could link them to the stored samples and/or results of tests run on their samples. This could cause a problem with insurance or getting a job.

iii. *Genetic Testing Risks:*
A possible risk is the accidental release of the subject's protected health information that could link them to the stored samples and/or results of the tests run on their samples. This may cause problems with insurance or getting a job, however, the Genetic Information Nondiscrimination Act of 2008 should help to protect our research subjects against such problems.

iv. *Data Collection Risks:*
There is no risk to subjects for participation other than the potential violation of confidentiality. Some questionnaires may be time consuming or tiring for the patients, but the subjects may suspend the interview if necessary or to review their participation at any time during the study. Some questions might make the participant uncomfortable due to the sensitivity of these questions.

B. Benefits:
There is no direct benefit to subjects for enrollment in the registry. However, information gained from the registry may provide knowledge that will be helpful in the care of future cardiovascular patients. Because the procedures in this study are to explore research aims, no results obtained from analysis of the blood samples and study data will be returned to the participants.

7.0 ADVERSE EVENTS/UNANTICIPATED PROBLEMS

Adverse events occurring from blood draw or breach of confidentiality will be reported to the IRB per institution guidelines. Because this is an observational study (i.e. we are observing the subject's normal course of disease and standard care) no other reporting of adverse events will be implemented (i.e. a report would not be filed if a subject expires due to the normal progression of disease). Recording of Adverse Events will start after the participant has signed the informed consent form. Adverse events must be documented by the Participating Sites in REDCap on a continuous basis.

Designated study staff at the Cardiovascular-Oncology Coordinating Center will monitor adverse event reporting by Participating Sites. They will confirm that adverse event reports were indeed sent to the IRB, as necessary, as well as monitor the frequency of adverse event occurrence to ensure that the aforementioned minimal risk of this study is maintained.

8.0 STUDY WITHDRAWAL/DISCONTINUATION

Subjects may withdraw from the study at any time. Subjects may request their biological samples to be destroyed at any time. However, any data or biological samples that have already been used for research cannot be destroyed. Subjects may also specify that they no longer wish to be contacted for annual follow-ups, but will allow the registry to retain any data and/or samples collected retrospectively.

The PI at each site may withdraw any participant at any time.

9.0 SURVIVE SUPERVISORY COMMITTEE

A SURVIVE Supervisory Committee will be established to evaluate the scientific merit of protocol proposal/applications that have been submitted to utilize any portion of data and/or specimens from the SURVIVE Registry and to assess the availability of the data/samples requested. The primary responsibility of the Supervisory Committee is to evaluate the scientific merit of submitted protocol applications and approve study protocols to use the SURVIVE Registry information and/or specimens.

A. Membership

SURVIVE Supervisory Committee membership will be made up of each Principal Investigator at each participating site, the Director of the SURVIVE Biobanking Core Lab, and the Director of the SURVIVE Imaging Core Lab. Each member is willing to participate in the collaboration effort to this joint venture and is agreeable to sharing resources collected within their own registry in the manner outlined below.

The SURVIVE Supervisory Committee will be comprised of contributing members with expertise in the field of cardiovascular medicine and its subspecialties (including heart failure, interventional cardiology, inherited heart disease, electrophysiology, cardiac imaging, as well as expertise in core laboratory process and data analysis) and/or hematology/oncology and its subspecialties. The SURVIVE Supervisory Committee members will nominate and selected the contributing members from international collaborators with proven interest and expertise in the discipline of cardio-oncology.

The contributing SURVIVE Supervisory Committee members are expected to serve for 3 years. Prior to the end of three years, members may rotate out or choose to continue participation. If a member is unable or unwilling to continue to serve, the reason will be documented and a replacement will be selected by the SURVIVE Supervisory Committee.

B. Responsibilities of the SURVIVE Supervisory Committee

i. *Project Review and Consideration:*
The SURVIVE Supervisory Committee member, who is also the PI (or designee) of the each participating site's registry, will conduct an initial, in-depth review of the proposal in a timely fashion and must be in agreement with the project use of the data/samples prior to the request being reviewed by the SURVIVE Supervisory Committee, as a whole.

All SURVIVE Supervisory Committee members will familiarize themselves with proposed research protocol, and analyze their scientific merit, feasibility, and use of the SURVIVE Registry data and resources.

A minimum of five SURVIVE Supervisory Committee members will discuss the merits of each proposed study, to reach a quorum. The Director of the SURVIVE Biobanking Core Lab and the Director of the SURVIVE Imaging Core Lab may also be in attendance, as needed, but will not count towards the quorum as they will be nonvoting members of the committee.

SURVIVE Supervisory Committee members may consult other faculty members with particular expertise in an area of research during protocol analysis.

A SURVIVE Supervisory Committee member or administrator will review and confirm that IRB approval has been granted for the proposed research prior to releasing data and specimens to the requestor.

The SURVIVE Supervisory Committee will review major proposed modifications in the study prior to their implementation/release of data and/or specimens through an amendment submission process.

Following each SURVIVE Supervisory Committee meeting, the Supervisory Committee will provide the study applicant with written determination of approval or disapproval to use the data/specimens from the SURVIVE Registry.

The SURVIVE Supervisory Committee will strive to complete the review of each proposed study within two weeks of submission, and provide the investigator with an estimation of the date when the data will be available.

ii. *Meetings*

The SURVIVE Supervisory Committee will meet prior to the approval of any applications for use of data/samples from the SURVIVE Registry. New members will review the SURVIVE Supervisory Committee charter, each registry's protocol, establish a meeting schedule, and review the study approvals and termination guidelines. The SURVIVE Supervisory Committee will meet at least quarterly. *Ad hoc* meetings may also be convened, if necessary, to facilitate application reviews. Formal meetings and *ad hoc* meetings may be held by teleconference; this will be decided on a case by case basis.

iii. *Recommendations from the SURVIVE Supervisory Committee*

SURIVIVE Supervisory Committee recommendations on study proposals are based on the scientific merit, cardiovascular-oncology registry mission, and resource feasibility of each protocol. Approval decisions will be conveyed to the investigator/applicant within two days of the meeting. If the application is rejected, recommendations will be made in order for the investigator to improve the protocol and better understand the rationale for the decision.

iv. *Data/Sample Release*

The core SURVIVE Supervisory Committee member (or designee), of each individual site registry who will be releasing the requested and approved data/samples, will be responsible for data and sample identification and communication with the Director of the SURVIVE Biobanking Core Lab for data and/or sample release. The PI (or designee) will be responsible for the integrity of the data and the manner in which it is released. Sample integrity will be the responsibility of the SURVIVE Biobanking Core Lab or the individual PI's lab, as applicable.

v. *Conflict of Interest*
Members of the SURVIVE Supervisory Committee will disclose any potential conflicts of interest, whether real or perceived, to other members. Examples of this would be protocols submitted by a SURVIVE Supervisory Committee member. In such a case, the member will recuse him/herself from the review process.

vi. *Amendment Submission*
If a SURVIVE Supervisory Committee approved project requires a significant change in scope or change in the amount of data/sample required to complete the project, the investigator will submit a new, amended request with the new information for consideration and review. Again, the individual PI (or designee) of the site registry will complete an initial review, followed by the full SURVIVE Supervisory Committee review prior to approval.

vii. *Confidentiality*
No communication, either written or oral, regarding the deliberations or recommendations of the SURVIVE Supervisory Committee will be made outside of the committee except as provided for by this guideline. Each member of the SURVIVE Supervisory committee will agree to uphold this statement.

viii. *Additional Information*
The SURVIVE Supervisory Committee member may obtain additional information pertaining to the individual protocols and IRB applications by contacting the SURVIVE Registry Administrator. This information will be made available to all members of the committee.

10.0 PARTICIPATING SITES

Potential Participating Sites that have been identified by the Cardiovascular-Oncology Coordinating Center's Principal Investigator, Dr. Daniel Lenihan, will be sent an invite letter for the study. If those sites agree to the terms of the study, they will be considered a Participating Site for the SURVIVE Registry.

The Cardiovascular-Oncology Coordinating Center will be looking to include at least 10 Participating Sites to start. If startup and enrollment at these Participating Sites is successful, the Cardiovascular-Oncology Coordinating Center will evaluate the feasibility of future site development and expansion of the number of Participating Sites for the SURVIVE Registry.

The anticipated Participating Sites at the startup of the SURVIVE Registry will include:

- Brigham & Women's Hospital
- Duke University
- Franciscan St. Francis Health
- The Mayo Clinic
- Stanford University Medical Center
- University of British Columbia
- University of Kansas Medical Center
- University of Pennsylvania
- University of South Florida Health
- University of Texas Southwestern
- Vanderbilt University School of Medicine
- MedStar Health

11.0 STATISTICAL CONSIDERATIONS

It is anticipated that the Cardiovascular-Oncology Coordinating Center will enroll approximately 250 patients in the first year, while Participating Sites will enroll approximately 50 patients per site in the first year. The number of patients enrolled in the study overall will be unlimited.

After three years of enrollment, the SURVIVE Supervisory Committee and the IRB will determine feasibility of continued enrollment in the SURVIVE Registry.

The study aims to collect as large a cohort of patients who have evidence of cardiovascular dysfunction and have been or are being treated for cancer. The statistical power will depend on the resultant final size of the study population and the questions that arise in subsequent studies submitted for SURVIVE Supervisory Committee and IRB approval.

Data will be stored in a WUSTL REDCap-supported database and transformed into a SAS, STATA, SPSS, R, excel, or CSV dataset and analyzed using SAS, STATA, SPSS or R software package.

12.0 PRIVACY/CONFIDENTIALITY ISSUES

Patients will sign informed consent. All data will be entered and stored in a REDCAP relational database, in turn stored in a secure, password protected and encrypted WUSTL website. Only study personnel will have access to the database. The data will not reside on any publically accessible computer. Restricted access to the database and site datasets will be made available only to that site's study personnel.

All standard measures to maintain confidentiality will be observed. This will be implemented by allowing only designated study staff to have access to identifiable information. To prevent accidental release of the results run on the participants' biological samples, these samples will be given a code. The specimen tubes will only

include an assigned barcode. Only designated study staff will have access to the decoding list. The name that belongs to the code will be kept in a locked file or in a computer with a password. Only designated research staff will have access to the subject's name or other identifying information. All written data forms for this study will be kept in a locked cabinet where only the designated study staff will have access.

Any publication resulting from the utilization of registry data will not identify any of the subjects by name or any other personal or hospital identifier.

13.0 REFERENCES

1. Oeffinger KC, Mertens AC, Sklar CA et al. Chronic health conditions in adult survivors of childhood cancer. N Engl J Med 2006;355:1572-82.
2. Miller KD, Siegel RL, Lin CC et al. Cancer treatment and survivorship statistics, 2016. CA Cancer J Clin 2016;66:271-89.
3. Cardinale D, Colombo A, Lamantia G et al. Anthracycline-induced cardiomyopathy: clinical relevance and response to pharmacologic therapy. J Am Coll Cardiol 2010;55:213-20.
4. Cardinale D, Colombo A, Bacchiani G et al. Early detection of anthracycline cardiotoxicity and improvement with heart failure therapy. Circulation 2015;131:1981-8.
5. Li W, Croce K, Steensma DP, McDermott DF, Ben-Yehuda O, Moslehi J. Vascular and Metabolic Implications of Novel Targeted Cancer Therapies: Focus on Kinase Inhibitors. J Am Coll Cardiol 2015;66:1160-78.
6. Ky B, Vejpongsa P, Yeh ET, Force T, Moslehi JJ. Emerging paradigms in cardiomyopathies associated with cancer therapies. Circulation research 2013;113:754-64.
7. Groarke JD, Cheng S, Moslehi J. Cancer-drug discovery and cardiovascular surveillance. N Engl J Med 2013;369:1779-81.
8. Hall PS, Harshman LC, Srinivas S, Witteles RM. The frequency and severity of cardiovascular toxicity from targeted therapy in advanced renal cell carcinoma patients. JACC Heart failure 2013;1:72-8.
9. Thakur A, Witteles RM. Cancer therapy-induced left ventricular dysfunction: interventions and prognosis. Journal of cardiac failure 2014;20:155-8.
10. Guarneri V, Lenihan DJ, Valero V et al. Long-term cardiac tolerability of trastuzumab in metastatic breast cancer: the M.D. Anderson Cancer Center experience. J Clin Oncol 2006;24:4107-15.
11. Ewer MS, Vooletich MT, Durand JB et al. Reversibility of trastuzumab-related cardiotoxicity: new insights based on clinical course and response to medical treatment. J Clin Oncol 2005;23:7820-6.
12. Telli ML, Hunt SA, Carlson RW, Guardino AE. Trastuzumab-related cardiotoxicity: calling into question the concept of reversibility. J Clin Oncol 2007;25:3525-33.
13. Ewer MS, Suter TM, Lenihan DJ et al. Cardiovascular events among 1090 cancer patients treated with sunitinib, interferon, or placebo: a comprehensive adjudicated database analysis demonstrating clinically meaningful reversibility of cardiac events. European journal of cancer (Oxford, England : 1990) 2014;50:2162-70.
14. Chu TF, Rupnick MA, Kerkela R et al. Cardiotoxicity associated with tyrosine kinase inhibitor sunitinib. Lancet 2007;370:2011-9.
15. Khakoo AY, Kassiotis CM, Tannir N et al. Heart failure associated with sunitinib malate: a multitargeted receptor tyrosine kinase inhibitor. Cancer 2008;112:2500-8.
16. Atrash S, Tullos A, Panozzo S et al. Cardiac complications in relapsed and refractory multiple myeloma patients treated with carfilzomib. Blood Cancer J 2015;5:e272.
17. Stewart AK, Rajkumar SV, Dimopoulos MA et al. Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. N Engl J Med 2015;372:142-52.

18. Grandin EW, Ky B, Cornell RF, Carver J, Lenihan DJ. Patterns of cardiac toxicity associated with irreversible proteasome inhibition in the treatment of multiple myeloma. Journal of cardiac failure 2015;21:138-44.

19. Armenian SH, Lacchetti C, Barac A et al. Prevention and Monitoring of Cardiac Dysfunction in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 2017;35:893-911.

20. Ezaz G, Long JB, Gross CP, Chen J. Risk prediction model for heart failure and cardiomyopathy after adjuvant trastuzumab therapy for breast cancer. Journal of the American Heart Association 2014;3:e000472.

21. Gulati G, Heck SL, Ree AH et al. Prevention of cardiac dysfunction during adjuvant breast cancer therapy (PRADA): a 2 x 2 factorial, randomized, placebo-controlled, double-blind clinical trial of candesartan and metoprolol. Eur Heart J 2016;37:1671-80.

22. Georgakopoulos P, Roussou P, Matsakas E et al. Cardioprotective effect of metoprolol and enalapril in doxorubicin-treated lymphoma patients: a prospective, parallel-group, randomized, controlled study with 36-month follow-up. Am J Hematol 2010;85:894-6.

23. Bosch X, Rovira M, Sitges M et al. Enalapril and carvedilol for preventing chemotherapy-induced left ventricular systolic dysfunction in patients with malignant hemopathies: the OVERCOME trial (preventiOn of left Ventricular dysfunction with Enalapril and caRvedilol in patients submitted to intensive ChemOtherapy for the treatment of Malignant hEmopathies). J Am Coll Cardiol 2013;61:2355-62.

24. Cardinale D, Colombo A, Lamantia G et al. Anthracycline-induced cardiomyopathy: clinical relevance and response to pharmacologic therapy. J Am Coll Cardiol 2010;55:213-20.

25. Plana JC, Galderisi M, Barac A et al. Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography 2014;27:911-39.

26. Ky B, Putt M, Sawaya H et al. Early increases in multiple biomarkers predict subsequent cardiotoxicity in patients with breast cancer treated with doxorubicin, taxanes, and trastuzumab. J Am Coll Cardiol 2014;63:809-16.

27. Cardinale D, Colombo A, Sandri MT et al. Prevention of high-dose chemotherapy-induced cardiotoxicity in high-risk patients by angiotensin-converting enzyme inhibition. Circulation 2006;114:2474-81.

14.0 APPENDICES

A. Sensitive Information Questionnaire

Please answer these questions to the best of your ability. There are no right or wrong answers. All information is kept strictly confidential.

1. Over the last 30 days, on average, how often did you have at least one alcoholic beverage?
An alcoholic beverage is considered one standard can or bottle of beer, malt liquor, or wine cooler [12 ounces], a standard glass of wine [4 ounces], a standard shot of liquor [1.5 ounces], or 1 mixed drink.
☐ Did not drink alcohol
☐ 1 day per week
☐ 2 days per week
☐ 3 days per week
☐ 4 days per week
☐ 5 days per week
☐ 6 days per week
☐ 7 days per week
☐ Prefer not to answer

2. Over the last 30 days, if you drank alcohol how many alcoholic beverages did you usually consume per occasion?
An alcoholic beverage is considered one standard can or bottle of beer, malt liquor, or wine cooler [12 ounces], a standard glass of wine [4 ounces], a standard shot of liquor [1.5 ounces], or 1 mixed drink.
☐ Did not drink alcohol
☐ 1-2 drinks
☐ 3-4 drinks
☐ 5-6 drinks
☐ More than 7 drinks
☐ Prefer not to answer

3. Have you ever been treated for alcoholism?
☐ No
☐ Yes
☐ Prefer not to answer

4. Have you ever used cocaine or other stimulants (eg. methamphetamine)?
Please check all that apply.
☐ Never
☐ Current use
☐ Past use
☐ I don't know
☐ Prefer not to answer

5. Please specify your ethnicity.
☐ Hispanic or Latino (*a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race*)
☐ Not Hispanic or Latino
☐ Prefer not to answer

6. What do you consider your race?
Please check all that apply.
☐ White/Caucasian (*a person having origins in any of the original peoples of Europe, the Middle East, or North* Africa)
☐ African-American/Black (*a person having origins in any of the black racial groups of Africa*)
☐ American Indian/Alaskan Native (*a person having origins in any of the original peoples of North and South America (including Central America), and who maintains tribal affiliation or community attachment*)
☐ Asian/Asian-American (*a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent*)
☐ Native Hawaiian/Other Pacific Islander (*a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands*)
☐ Other _____
☐ Prefer not to answer

7. What is the highest level of education you have completed?
☐ Less than 6th grade (less than elementary school)
☐ 6th – 8th grade (middle school)
☐ 9th – 11th grade (less than high school)
☐ 12th grade (high school)
☐ Some college
☐ College graduate
☐ Some graduate school
☐ Graduate school
☐ Prefer not to answer

8. What is your current job status?
☐ Working part time
☐ Working full time
☐ Unemployed but looking for work
☐ Unemployed and not looking for work
☐ Disabled
☐ Retired
☐ Other _____
☐ Prefer not to answer

9. If you are working, what is your current job?
Please fill in.

_____

10. What is your marital status?
☐ Never married
☐ Married
☐ Divorced
☐ Separated
☐ Widowed
☐ Prefer not to answer

11. What is your family income (in US Dollars)?
☐ Less than $10,000
☐ $10,000-$24,999
☐ $25,000-$49,999
☐ $50,000-$74,999
☐ $75,000-$99,999
☐ $100,000-$199,000
☐ More than $200,000
☐ Prefer not to answer

12. Besides yourself, who else lives in your household?
Please check all that apply.
☐ No one else
☐ Spouse
☐ Same sex domestic partner
☐ Children – minors
☐ Children – adults
☐ Other relatives
☐ Friends
☐ Prefer not to answer

13. Including yourself, how many total people live your household?
Please fill in.

_____

14. What best describes your type of residence?
Please mark the one that best applies.
☐ House
☐ Apartment/duplex/rental house
☐ Assisted living facility
☐ Nursing home facility
☐ Homeless
☐ Other _____
☐ Prefer not to answer

15. How many times per week do you exercise?
Exercise is defined as at least 30 minutes of aerobic activity at a time.
☐ Do not exercise
☐ 1 time per week
☐ 2 times per week
☐ 3 times per week
☐ 4 times per week
☐ 5 times per week
☐ 6 times per week
☐ 7 times per week
☐ Prefer not to answer

16. If you are not able to complete 30 minutes of aerobic activity, how many minutes can you complete?
Please fill in.

_____

17. How many times per week do you complete the number if minutes of aerobic activity you wrote for question 18?
☐ Do not exercise
☐ 1 time per week
☐ 2 times per week
☐ 3 times per week
☐ 4 times per week
☐ 5 times per week
☐ 6 times per week
☐ 7 times per week
☐ Prefer not to answer

18. What type of aerobic exercise did you do?
Please select all that apply.
☐ Do not exercise
☐ Light walk
☐ Light jog
☐ Brisk walk
☐ Brisk jog
☐ Biking
☐ Other _____
☐ Prefer not to answer

B. EuroQol 5D-5L (EQ-5D) Quality of Life Questionnaire

EQ-5D-5L

Health Questionnaire

English version for the USA

Under each heading, please check the ONE box that best describes your health TODAY

MOBILITY

- I have no problems walking ❑
- I have slight problems walking ❑
- I have moderate problems walking ❑
- I have severe problems walking ❑
- I am unable to walk ❑

SELF-CARE

- I have no problems washing or dressing myself ❑
- I have slight problems washing or dressing myself ❑
- I have moderate problems washing or dressing myself ❑
- I have severe problems washing or dressing myself ❑
- I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

- I have no problems doing my usual activities ❑
- I have slight problems doing my usual activities ❑
- I have moderate problems doing my usual activities ❑
- I have severe problems doing my usual activities ❑
- I am unable to do my usual activities ❑

PAIN / DISCOMFORT

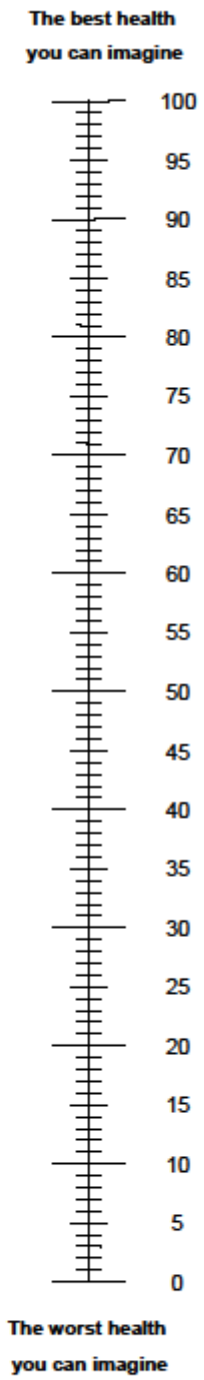
- I have no pain or discomfort ❑
- I have slight pain or discomfort ❑
- I have moderate pain or discomfort ❑
- I have severe pain or discomfort ❑
- I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

- I am not anxious or depressed ❑
- I am slightly anxious or depressed ❑
- I am moderately anxious or depressed ❑
- I am severely anxious or depressed ❑
- I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



3

C. Cardiovascular Risk Assessment Questionnaire

Please answer these questions to the best of your ability. There are no right or wrong answers. All information is kept strictly confidential.

1. Do you currently or have you ever smoked cigarettes?
☐ Yes, I am a current smoker
☐ No, I quit less than a year ago
☐ No, I quit more than a year ago
☐ No, I never smoked
☐ Prefer not to answer

2. How many cigarettes did you or do you smoke per day?
Please check all that apply.
☐ Do not smoke
☐ 1-10 cigarettes per day (10 cigarettes = ½ pack) for _____ years
☐ 11-20 cigarettes per day (20 cigarettes = 1 pack) for _____years
☐ 21-30 cigarettes per day (30 cigarettes = 1 ½ packs) for _____years
☐ 31-40 cigarettes per day (40 cigarettes = 2 packs) for _____years
☐ More than 41 cigarettes per day (more than 2 packs) for _____years
☐ Prefer not to answer

3. How many minutes of moderate physical activity do you get in a week?
A person doing moderate physical activity can usually talk, but not sing, during the activity. Please fill in.

_____ minutes of moderate activity

4. How many minutes of vigorous physical activity do you get in a week?
A person doing vigorous physical activity usually cannot say more than a few words before pausing for a breath. Please fill in.

_____ minutes of moderate activity

5. How many cups of fruits and vegetables do you eat in an average day?
<u>One cup of fruit</u> = 1 banana, 1 apple, 15 grapes, or ½ cup raisins
<u>One cup of vegetables</u> = 1 ear of corn, 1 potato, 2 cups cooked greens, 1 cup uncooked greens, 2 celery stalks, or 12 baby carrots
☐ Less than 4 ½ cups
☐ 4 ½ cups or more
☐ I don't know
☐ Prefer not to answer

6. Do you eat 2 servings or more of fish weekly?
One serving of fish is approximately 3.5 ounces, approximately the size of a deck of cards.
☐ Yes
☐ No
☐ I don't know
☐ Prefer not to answer

7. Do you eat 3 or more servings of whole grains daily?
Whole grain foods include whole wheat or rye bread, brown or wild rice, whole-wheat pasta, bran flakes or whole-grain cereals, and oatmeal.
☐ Yes
☐ No
☐ I don't know
☐ Prefer not to answer

8. Do you drink less than 36 ounces (4 ½ cups) of beverages with added sugar weekly?
Beverages with added sugar include: regular soft drinks, fruit drinks (fruitaides and fruit punch), and sweet tea.
☐ Yes
☐ No
☐ I don't know
☐ Prefer not to answer

9. Do you eat 1,500 milligrams or less of sodium daily?
If you don't track your daily sodium intake by reading the food label, to answer "yes" you should do at least two of the following:

- *Avoid eating pre-packaged processed food or eat low-sodium versions.*
- *Avoid eating out or ask for low-sodium preparations.*
- *Cook at home without adding salt.*

☐ Yes
☐ No
☐ I don't know
☐ Prefer not to answer