A Safety and Feasibility Study of Limited Cardiac Monitoring during Non-anthracycline Trastuzumab-based Therapy in Patients with HER2-positive Breast Cancer

PROTOCOL FACE PAGE FOR MSK NON THERAPEUTIC PROTOCOL

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Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.

OneMSK Sites	
Manhattan	All Protocol Activities
Basking Ridge	Consent and Follow-Up
Bergen	Consent and Follow-Up
Commack	Consent and Follow-Up
Nassau	Consent and Follow-Up
Monmouth	Consent and Follow-Up
Westchester	Consent and Follow-Up

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

Study Title:	A Safety and Feasibility Study of Limited Cardiac Monitoring during Non-anthracycline Trastuzumab-based Therapy in Patients with HER2-positive Breast Cancer
Study Objectives:	Primary Objective: To evaluate the cardiac safety of a limited cardiac monitoring strategy in patients with HER2-positive breast cancer treated with a non-anthracycline trastuzumab-based regimen. Secondary Objectives: 1) To determine the feasibility of a limited cardiac monitoring strategy 2) To measure the absolute change in left ventricular ejection fraction (LVEF) at 6 and 12 months after initiation of trastuzumab 3) To measure the absolute change in global longitudinal strain (GLS) at 6 and 12 months after trastuzumab 4) To estimate the incidence of trastuzumab-based treatment interruption attributed to cardiac causes 5) To estimate the incidence of asymptomatic LVEF decline during trastuzumab 6) To evaluate health service utilization
Patient population:	Patients with HER2-positive breast cancer (stage I-IV) planned to undergo treatment with a non-anthracycline trastuzumab-based regimen
Number of patients:	194 patients
Inclusion criteria:	All patients must meet the following criteria: • Female • Age ≥ 18 years • Newly diagnosed histologically confirmed primary invasive breast carcinoma (Stage I-IV) • Pathologically confirmed HER2-positive breast cancer • Planned to receive trastuzumab-based therapy for at least 12 months, or started trastuzumab within the last 6 weeks with a planned duration of at least 12 months • Normal LV systolic function • Willing and able to comply with the requirements of the protocol
Exclusion criteria:	Patients are to be excluded from the study if they meet any of the following criteria: • Planned to receive an anthracycline-based regimen • Prior history of treatment with anthracycline chemotherapy • History of cardiovascular disease including cardiomyopathy, heart failure, or any other clinically significant cardiovascular disease (as deemed by the investigator) • Uncontrolled hypertension, defined by BP > 160/90
Design:	This study will enroll 190 evaluable women with HER2-positive breast cancer (stage I-IV) at low cardiotoxicity risk, defined as: 1) no history of HF or cardiomyopathy; 2) normal LV systolic function; and 3) no previous anthracycline exposure. Patients enrolled in this study will be treated with a non-anthracycline trastuzumab-based regimen, at the discretion of the

	treating medical oncologist. Participants will follow a limited cardiac monitoring strategy consisting of a LVEF assessment at baseline, 6 months, and 12 months. Safety will be evaluated by the cumulative incidence of severe HF (New York Heart Association class III/IV) or cardiac death at 12 months after trastuzumab.
Time to completion	We expect to enroll 1-2 patients every week and aim to complete enrollment in 3 years.

2.0 OBJECTIVES AND SCIENTIFIC AIMS

Primary Objective: To evaluate the cardiac safety of a limited cardiac monitoring strategy in patients with HER2-positive breast cancer treated with a non-anthracycline trastuzumab-based regimen.

Secondary Objectives:

1) To determine the feasibility of a limited cardiac monitoring strategy
2) To measure the absolute change in LVEF at 6 and 12 months after initiation of trastuzumab-based therapy
3) To measure the absolute change in global longitudinal strain at 6 and 12 months after trastuzumab-based therapy
4) To estimate the incidence of trastuzumab-based treatment interruption attributed to cardiac causes
5) To estimate the cumulative incidence of asymptomatic LVEF decline during trastuzumab-based therapy
6) To evaluate health service utilization

3.0 BACKGROUND AND RATIONALE

Trastuzumab-based cancer treatment substantially improves survival but is associated with a risk of acute cardiotoxicity. Breast cancer is the most commonly diagnosed cancer in women, and the 2nd leading cause of cancer death in women. Approximately 20-30% of invasive breast cancers over-express the human epidermal growth factor receptor 2 (HER2) oncogene, which is associated with a more aggressive cancer phenotype and poor prognosis.(1,2) Treatment with trastuzumab (Herceptin), a humanized monoclonal antibody against the extracellular domain of HER2, has improved outcomes of patients with HER2-positive breast cancer. Chemotherapy in combination with sequential trastuzumab in the adjuvant setting has significantly reduced the risk of recurrence by 40-50% and the risk of all-cause death by 33%.(3-5) However, because HER2 plays an important role in the normal stress response of cardiomyocytes,(6) treatment with trastuzumab has been associated with increased risk of cardiotoxicity. In the pivotal clinical trials of sequential trastuzumab after completion of adjuvant chemotherapy (mostly anthracycline-based), the rate of severe [New York Heart Association (NYHA) class III or IV] heart failure (HF) ranged from 0.5% to 4.1%.(3-5,7)

Routine cardiac imaging is currently recommended to monitor for cardiotoxicity during breast cancer treatment. Several safeguards were implemented during clinical trials of trastuzumab following anthracycline-based chemotherapy with the overall goal of minimizing cardiotoxicity. These included monitoring of LVEF at baseline and at 3-month intervals during

trastuzumab as well as strict LVEF-based criteria for interruption or discontinuation of trastuzumab.(8) In 2006, the FDA approved trastuzumab for the treatment of HER2-positive breast cancer in the adjuvant setting and recommended that routine LVEF monitoring be performed at baseline and every 3 months.(9) This recommendation has subsequently been endorsed by the NCCN guidelines.(10) Based on a standard-of-care treatment regimen with trastuzumab administered for 1 year, this translates to an echocardiogram performed at baseline and months 3, 6, 9, and 12. With nearly 10 years of long-term cardiac follow-up data, we have gained a better understanding of the incidence, risk factors, and natural history of trastuzumab cardiotoxicity.(8,11-16) Treatment with anthracycline chemotherapy has consistently been identified as a major risk factor for trastuzumab cardiotoxicity.(17-19)

Use of non-anthracycline trastuzumab-based regimens for treatment of HER2-positive breast cancer is rising. Anthracycline chemotherapy has been the mainstay of breast cancer treatment since the 1980s, but its role has come under scrutiny given the risk of cardiotoxicity, particularly when given with trastuzumab, as well as the development of non-anthracycline regimens with improved cardiac safety.(5,20) For example, a multi-center clinical trial has demonstrated significant efficacy of paclitaxel and trastuzumab for the treatment of low risk HER2-positive breast cancer.(21) The risk of cardiotoxicity from these non-anthracycline trastuzumab-based regimens is low, estimated to be ~0.5% based on two clinical trials of nearly 1,000 women.(21-23) Our data from a retrospective cohort study of 165 real world patients treated at MSK with a non-anthracycline trastuzumab–based regimen revealed only 2 patients (1.2%) with severe HF events, both with multiple risk factors for cardiotoxicity (one with a low baseline LVEF < 53%, and one with prior exposure to anthracycline chemotherapy).(24) Current trends in breast cancer treatment reflect a rising concern for cardiac toxicity from anthracycline-based regimens. In a Medicare study, breast cancer treatment with anthracycline-based chemotherapy decreased from ~70% in 2005 to 32% in 2008.(25) At MSK, nearly 50% of patients currently receive a non-anthracycline based regimen for treatment of HER2-positive breast cancer.

Despite the low risk of cardiotoxicity in patients receiving non-anthracycline trastuzumab-based regimens, current cardiac monitoring recommendations continue to use a one-size-fits-all approach. In patients treated without anthracyclines, routine cardiac monitoring is less likely to alter treatment decisions or impact patient outcomes given the inherently lower cardiotoxicity risk associated with these regimens. Nonetheless, a uniform one-size-fits-all recommendation for cardiac monitoring applies to all patients treated with trastuzumab-based therapy regardless of the specific treatment regimen (anthracycline versus non-anthracycline). This raises the question of whether current cardiac monitoring guidelines should be modified to take into account the variability and improved cardiac safety profile of trastuzumab regimens in use today, with intensive serial cardiac monitoring reserved for patients at increased cardiotoxicity risk.(21,25)

Overscreening for cardiotoxicity may lead to poorer cancer outcomes. 2D echocardiography is the primary modality used for cardiac monitoring during breast cancer treatment. However, this technique has several limitations including temporal, inter- and intra-observer variability that can range from 10% to 13%.(26) This may result in the detection of false positive results that require additional time and testing to resolve or LVEF declines that are transient and of limited clinical

significance. The risk is that some patients will be incorrectly labeled as having cardiotoxicity, leading to interruption or early termination of curative therapy. In a retrospective cohort study that we performed in 585 women with HER2-positive breast cancer, we found that premature trastuzumab interruption was significantly associated with breast cancer recurrence and disease free survival.(27) These findings are consistent with a recent population based-study of 3,134 women treated with adjuvant trastuzumab, in which patients receiving 1-8 (< 6 months) and 9-15 (6-12 months) doses of trastuzumab had a higher risk of breast cancer recurrence (HR 3.09 and 2.39, respectively) and mortality (HR 2.41 and 2.85, respectively) compared to patients receiving ≥ 16 (≥ 12 months) doses of trastuzumab.(28) Efforts to identify the most beneficial and least harmful cardiac monitoring strategy during trastuzumab-based treatment are therefore critical to improving patient outcomes.

Unnecessary medical testing plays a major role in the rising cost of healthcare. Based on a report by the Institute of Medicine, unnecessary health spending constitutes approximately 30% of all healthcare spending.(29) With an estimated 20% of ~240,000 patients diagnosed with breast cancer per year having HER2-positive breast cancer, the projected annual cost for cardiac monitoring based on current recommendations for routine cardiac monitoring every 3 months exceeds $60 million. There is a need to critically examine the current standard practice of routine cardiac monitoring during trastuzumab therapy, and instead replace it with an evidence-based strategy that ensures the highest level of cardiac safety during trastuzumab treatment without jeopardizing cancer outcomes or incurring unnecessary medical expense. Failure to do so prevents any improvement in the quality of care delivered to patients with breast cancer and contributes to the rising cost of healthcare. In this project, we seek to explore and develop new knowledge on the safety and benefits of less cardiac monitoring during trastuzumab-based therapy and establish evidence that can be used to inform patient care.

Focusing on patients with HER2-positive breast cancer treated with non-anthracycline trastuzumab-based regimens and at low risk for cardiotoxicity will give us a unique opportunity to explore an alternative cardiac monitoring strategy. Routine cardiac monitoring may be unjustified in low-risk patients and expose them to the harms of false-positive results, potential interruption or discontinuation of curative therapy, and unnecessary healthcare expenditures. A limited schedule of cardiac monitoring, as proposed in the current study, poses a potential risk that trastuzumab may be continued without interruption despite an asymptomatic LVEF decline. However, existing recommendations for routine cardiac monitoring lack evidence, and there is no data to show that routine cardiac monitoring performed every 3 months is associated with improved cardiovascular outcomes. The incidence of asymptomatic LVEF decline for non-anthracycline trastuzumab regimens is low (~3%) and our preliminary data suggests that continuous trastuzumab may be safe in patients with asymptomatic LVEF decline.[48] Furthermore, the median number of LVEF assessments performed in our prior retrospective study of HER2-positive breast cancer patients treated with paclitaxel and trastuzumab was 3 (range 1 to 5), indicating that outside of a clinical trial setting many providers are already following a strategy of limited cardiac monitoring.(30) Despite the decreased frequency of cardiac monitoring, the rate of severe HF events (1.1%) was similar to rates published in clinical trials with routine cardiac monitoring. Existing data on the low cardiac event rate with non-anthracycline trastuzumab-based regimens combined with our preliminary data showing no increase in cardiac events with

decreased cardiac monitoring provides the rationale and preliminary safety data for the proposed study.

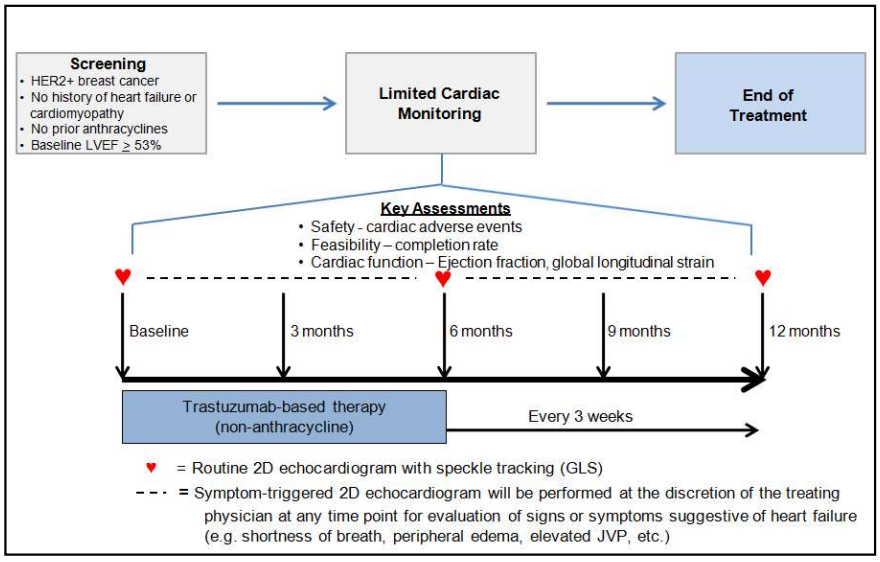
4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

This single-arm study will assess the cardiac safety of a limited cardiac monitoring strategy in patients with HER2-positive breast cancer treated with non-anthracycline trastuzumab-based therapy.

4.2 Intervention

Participants will undergo a LVEF assessment at baseline (pre-treatment) and at 6 and 12 months after initiation of trastuzumab-based therapy. For patients with metastatic breast cancer, after the 12-month period on study, LVEF monitoring will continue per physician's discretion off study while on trastuzumab-based therapy. The primary endpoint is cardiac safety, defined by a severe heart failure event (NYHA class III or IV) or cardiac death. Secondary endpoints to be evaluated include feasibility (as determined by the proportion of patients who successfully comply witha limited cardiac monitoring strategy during trastuzumab based therapy, absolute change in LVEF and GLS at 6 and 12 months after initiation of trastuzumab-based therapy, incidence of trastuzumab-based therapy interruption for cardiac reasons, incidence of asymptomatic LVEF decline, and utilization of healthcare resources.



5.0 CRITERIA FOR SUBJECT ELIGIBILITY

Describe the characteristics of the subject population.

5.1 Subject Inclusion Criteria

- Female
- Age ≥ 18 years

- Newly diagnosed histologically confirmed primary invasive breast carcinoma (Stage I-IV)
- Pathologically confirmed HER2-positive breast cancer
- Planned to receive trastuzumab-based therapy for a minimum of 12 months, or started trastuzumab-based therapy within the last 6 weeks weeks with a planned duration of at least 12 months
- Normal LV systolic function (EF greater than or equal to the institutional lower limit of normal)
- Willing and able to comply with the requirements of the protocol

5.2 Subject Exclusion Criteria

- Planned to receive an anthracycline-based regimen
- Prior history of treatment with anthracycline chemotherapy
- History of cardiovascular disease including cardiomyopathy, heart failure, or any other clinically significant cardiovascular disease (as determined by the investigator)
- Uncontrolled hypertension, defined as systolic blood pressure $\geq$ 160 mmHg and/or diastolic blood pressure $\geq$ 90 mmHg (as determined by the investigator).

6.0 RECRUITMENT PLAN

A member of the patient's treatment team, the protocol investigator, or research team at MSK will identify potential research participants. The preliminary screen of eligibility will be confirmation of the diagnosis of HER2-positive breast cancer. A member of the treatment team will discuss the study and the possibility of enrollment in the study with potential subjects that meet this eligibility criterion. The study will be conducted at the Evelyn H. Lauder Breast Center of MSK as well as at the regional MSK network sites. Recruitment at both main and regional network sites will ensure the enrollment of diverse populations of different ages, races, and ethnic groups onto the study. Patients will then be consented to the study.

In most cases, the initial contact with the prospective subject will be conducted either by the treatment team, investigator or the research staff working in consultation with the treatment team. The recruitment process outlined presents no more than minimal risk to the privacy of the patients who are screened and minimal PHI will be maintained as part of a screening log. For these reasons, we seek a (partial) limited waiver of authorization for the purposes of (1) reviewing medical records to identify potential research subjects and obtain information relevant to the enrollment process; (2) conversing with patients regarding possible enrollment; (3) handling of PHI contained within those records and provided by the potential subjects; and (4) maintaining information in a screening log of patients approached.

During the initial conversation between the investigator/research staff and the patient, the patient may be asked to provide certain health information that is necessary for the recruitment and enrollment process. The investigator/research staff may also review portions of their medical records at MSKCC in order to further assess eligibility. If the patient turns out to be ineligible for the research study, the research staff will destroy all information collected on the patient during the initial conversation and medical records review, except for any information that must be maintained for screening log purposes.

All recruited patients will be under the care of an attending medical oncologist. Patients will be accrued to this study without regard for minority status. The study will be available to the public and the details of the inclusion criteria, exclusion criteria and study design will be posted at www.clinicaltrials.gov. The principal investigator, Dr. Anthony Yu, will be available to all patients for further questions and information through a contact number which is provided on the consent form.

7.0 ASSESSMENT/EVALUATION PLAN

The study investigators and research study personnel will assess and confirm the eligibility of each patient. All screening procedure results and relevant medical history must be available before eligibility can be determined. Patients consented who do not subsequently meet eligibility criteria will be registered as a screen fail and will be replaced.

All patients will receive trastuzumab-based therapy at the discretion of the medical oncologist in the outpatient setting. Participants will undergo 3 LVEF assessments during the treatment period—at baseline, 6 months after initiation of trastuzumab, and 12 months after initiation of trastuzumab. For patients with stage I-III disease, 12 months of trastuzumab is considered a complete course of treatment, whereas patients with stage IV disease may receive additional trastuzumab beyond 12 months. Additional cardiac assessments may be performed at the discretion of the treating provider for evaluation of possible signs or symptoms of HF, such as worsening exertional dyspnea, orthopnea, peripheral edema, S3 gallop, elevated jugular venous pressure (JVP), or pulmonary edema. Symptoms suggestive of heart failure will prompt a cardiology consultation. All study assessments are described below:

7.1 CV (Cardiac) Questionnaire (Appendix A): At baseline a cardiac questionnaire will be completed by the patient, with assistance from research study personnel, to document cardiac medical history

7.2. 2D and Doppler Echocardiogram with speckle tracking strain: Conventional 2D and Doppler echocardiograms will be performed per protocol using a commercially available ultrasound scanner, according to the American Society of Echocardiography (ASE) recommendations for a comprehensive examination.(31) For patients who are enrolled at the Evelyn H. Lauder Breast Center, LVEF assessments will be performed by 2D echocardiography using the Vivid 7 or E9 system (GE Healthcare, Milwaukee, WI). Patients enrolled at a regional network site will undergo LVEF assessment by 2D echocardiography at a local cardiac imaging facility, and digital echocardiographic recordings stored in DICOM format will be reviewed at MSK for central analysis. At baseline, a LVEF greater than or equal to the lower limit of normal is required for entry onto the study.

Speckle tracking-based global longitudinal strain (GLS) measurements will be obtained from 3 apical views acquired during the standard 2D echocardiogram using standard commercially available vendor independent software (2D Cardiac Performance Analysis, TomTec Imaging Systems, Munich, Germany).(32) This analysis will be performed independent of the clinical interpretation of the 2D echocardiogram. A parasternal short axis view at the level of the papillary muscle will be used to obtain peak global radial and circumferential systolic strain and strain rate. All echocardiograms will be analyzed by a single echocardiographer (Yu, PI).

7.3. Cardiovascular assessments on study: A study worksheet (Appendix B) will be completed by the treating medical oncologist and/or member of the research team every 3 months during routine clinical visits to assess for cardiac adverse events and serious adverse events.

7.4. MSK health service utilization: Total healthcare resource utilization for hospitalizations, emergency room visits, physician visits, imaging and laboratory studies, and pharmacy services will be abstracted from MSK institutional billing records beginning 3 months prior to the initiation of trastuzumab to 6 months after the date of final trastuzumab. Healthcare resource utilization and costs will be classified into cardiovascular-related and non-cardiovascular-related costs by identifying billing records associated with cardiovascular-specific diagnoses or procedure codes. If a cardiovascular diagnosis was the primary reason for any hospitalization or emergency room visit, all resource utilization and costs from that encounter will be considered cardiovascular-related. Medicare reimbursement rates will be used as a proxy for direct medical costs.(33) Healthcare costs will be estimated by multiplying resource use with the corresponding unit cost values. Mean per patient costs will be estimated for total healthcare and cardiovascular-related resource utilization during the study period.

7.5. Non-MSK health service utilization: To ascertain use of non-MSK healthcare resources and patient out-of-pocket spending, we will administer a health service utilization questionnaire (HSUQ) during visits at months 3, 6, 9, and 12 after starting trastuzumab-based therapy and at 6 months after end of treatment(Appendix C). The questionnaire was developed by Dr. Elkin and modeled after existing healthcare utilization instruments. The HSUQ was adapted specifically for this study, although is based on existing health service utilization instruments. It will ask patients about their use of prescription and non-prescription medications, physician visits, hospital stays, and other medical services received outside of MSK (34). The HSUQ will be filled out directly by the patient in REDCap or on paper. For MSK Patients only.

7.6. Screening and assessments: The table below outlines the schedule of assessments applied to patients. All study assessments have a window of +/- 30 days unless otherwise noted. If the subject is unable to have a study assessment taken within the defined time window due to an event outside of his or her control (e.g. clinic closure, personal emergency, inclement weather, vacation) the assessment should be performed as close as possible to the required schedule.

Patients will follow the study intervention for a maximum of 12 months. Patients with stage IV disease may receive additional trastuzumab beyond 12 months, and further cardiac asessments beyond 12 months will be performed at the discretion of the treatment oncologist per standard of care. All patients will undergo a 6 month follow-up after end of treatment or after month 12.

Study Procedures	**Screening**	**Study Visits and Assessments**				**Follow-Up (6 months post-EOT)[6]**
		Month 3	**Month 6**	**Month 9**	**Month 12/EOT[5]**	
Informed consent	X					
Medical history	X	X	X	X	X	X
Physical exam	X	X	X	X	X	X

Vital Signs	X	X	X	X	X	X
CV Questionnaire	X					
Echocardiogram	X[3]		X[4]		X[4]	X[6]
HSUQ[1]		X	X	X	X	X
Study Worksheet		X	X	X	X	X
Cardiology consultation[2]		As needed	As needed	As needed	As needed	As needed

[1] Health services utilization questionnaire. For MSK Patients only.
[2] Cardiology consultation will be performed as needed for patients who develop signs or symptoms suggestive of cardiotoxicity, per standard of care
[3] Baseline echocardiogram should be performed within 3 months of registration. An alternative imaging modality (e.g. MUGA or cardiac MRI) will be accepted for LVEF assessment if it falls within the appropriate time frame.
[4] Follow-up echocardiograms should be performed +/- 6 weeks at the month 6 and 12 timepoints. An alternative imaging modality (e.g. MUGA or cardiac MRI) will be accepted for LVEF assessment if it falls within the appropriate time frame.
[5] End of treatment (EOT)
[6] Post EOT follow-up assessments should be performed +/- 3 months. An alternative imaging modality (e.g. MUGA or cardiac MRI) will be accepted for LVEF assessment in lieu of an echocardiogram if it falls within the appropriate time frame.

8.0 TOXICITIES/SIDE EFFECTS

The treating investigator or qualified designee will assess each subject to evaluate for potential new or worsening adverse effects as specified in the study flow chart (see section 7.3) and more frequently if clinically indicated. Toxicity grading will be performed in accordance with NCI CTCAE, V 5. Echocardiography is a standard of care test that is performed for routine cardiopulmonary assessment during trastuzumab-based therapy for breast cancer. No short- or long-term side effects are expected.

Management of symptomatic heart failure

Heart failure and left ventricular systolic dysfunction are known adverse effects of trastuzumab-based therapy. A complete listing of toxicities can be found in the trastuzumab package insert. Patients who develop signs and/or symptoms of HF should have trastuzumab-based therapy held and be referred to a cardiologist for treatment as recommended by the American Heart Association/American College of Cardiology.(35) Patients with a confirmed heart failure event will be removed from the study intervention and will no longer follow the limited cardiac monitoring schedule. These patients will be included in the evaluation of the primary endpoint and will undergo follow-up at 6 months post-end of treatment per protocol. Additional cardiac monitoring assessments should be performed at the consulting cardiologist's discretion.

Management of asymptomatic LVEF decline

Patients who experience an asymptomatic decrease in LVEF, defined as an absolute decline of LVEF > 10% from baseline to below the lower limit of normal, or an absolute decline of LVEF > 15%, should be referred to a cardiologist for further management. Consideration should be given to repeating a LVEF assessment at MSK within 1-2 weeks to confirm an observed LVEF decline, given the inherent variability of LVEF assessment. Additional trastuzumab-based therapy may be considered in patients experiencing an asymptomatic LVEF decline, at the discretion of the treating medical oncologist and consulting cardiologist.

- If trastuzumab is continued without interruption (or with interruption ≤ 6 weeks), repeat LVEF assessments should be performed at least every 6 weeks for 2 evaluations and then every 3 months thereafter, or as clinically indicated at the discretion of the consulting cardiologist.
- If trastuzumab is interrupted for > 6 weeks, repeat LVEF assessments during the interruption time period should be performed at the discretion of the consulting cardiologist. If LVEF improves and trastuzumab is reinitiated, repeat LVEF assessments should be performed every 6 weeks for 2 evaluations and then every 3 months thereafter, or as clinically indicated at the discretion of the consulting cardiologist.
- If trastuzumab is permanently discontinued, patients will be removed from the study intervention and will no longer follow the limited cardiac monitoring schedule. Repeat LVEF assessments should be performed at the discretion of the consulting cardiologist. These patients will undergo follow-up at 6 months post-end of treatment per protocol.

9.0 PRIMARY OUTCOMES

Primary outcome measurements:

The primary objective of this proposal is to evaluate the safety of a limited cardiac monitoring strategy in women with HER2-positive breast cancer treated with a non-anthracycline trastuzumab-based therapy. The primary cardiac safety endpoint will be a composite of a heart failure event (NYHA class III/IV) or death from cardiovascular causes attributable to trastuzumab therapy, defined as follows:

- A heart failure event (NYHA class III/IV) must meet the following criteria:
    1. The patient has an urgent unscheduled outpatient visit **OR** emergency department visit **OR** hospitalization with a primary diagnosis of heart failure.
    2. Patient exhibits new/worsening symptoms (e.g. shortness of breath, orthopnea, paroxysmal nocturnal dyspnea, decreased exercise tolerance, fatigue, other symptoms of volume overload) of heart failure associated with a reduced or mid-range LVEF (< 50%). Possible signs suggestiveof HF may include peripheral edema, abdominal distention, pulmonary rales, increased jugular venous pressure and/orhepatojugular reflux, S3 gallop, or rapid weight gain thought to be related to fluid retention, etc.. Possible laboratory findings suggestive of HF may include increased brain natriuretic peptide or radiologic evidence of pulmonary congestion.
    3. The patient receives initiation or intensification of treatment specifically for heart failure, including at least one of the following: a) oral diuretic therapy; b) intravenous diuretic or vasoactive agent (e.g. inotrope, vasopressor, or vasodilator); c) mechanical or surgical intervention including mechanical circulatory support (e.g. intra-aortic balloon pump, ventricular assist device, extracorporeal membrane oxygenation) or mechanical fluid removal (e.g. ultrafiltration, hemofiltration, dialysis).
    4. Patient experiences marked limitation of physical activity but is comfortable at rest (NYHA class III) **OR** is unable to carry on any physical activity without discomfort (NYHA class IV).

- Definite or probable cardiac death includes death resulting from acute myocardial infarction, sudden cardiac death, arrhythmia, heart failure, stroke, cardiovascular procedures, CV hemorrhage, or other CV causes.

The principal investigator will review all study worksheets to identify possible cardiac events. All participants with any HF symptoms reported on the study worksheet and all participants with a reduced LVEF < 50% will be reviewed and adjudicated for cardiac events independently by a panel of 2 cardiologists, listed on the face sheet of this study, blinded to each other's review. The PI will not be one of these cardiologists and will be responsible for facilitating the blinded review. The suspected relationship between a cardiac event to trastuzumab therapy will be ascertained by the 2 cardiology reviewers. A cardiac event will be considered attributable to trastuzumab if there is a plausible temporal relationship between the onset of the cardiac event and administration of trastuzumab-based therapy. A cardiac event in which there is evidence indicating an etiology unrelated to trastuzumab (e.g. pre-existing medical condition, underlying disease, intercurrent illness) will be considered not attributable to trastuzumab. Only cardiac events attributable to trastuzumab will contribute to the primary endpoint (Appendix D).

Cases in which there is disagreement will be reviewed by a third cardiologist, and a majority decision amongst the 3 cardiologists will be required to determine whether the criteria for a cardiac event were met. For the primary safety endpoint, all patients who received at least one dose of trastuzumab-based therapy will be considered evaluable. Patients who develop a confirmed cardiac event or prematurely discontinue trastuzumab for cardiac or non-cardiac reasons (before month 12) will be removed from continuing on study with the limited monitoring schedule but will be followed 6 months after end of treatment and will contribute to the primary endpoint evaluation.

Secondary outcome measurements – The secondary outcome measures for this study are as follows:

- Feasibility of a limited cardiac monitoring strategy will be evaluated by assessing the compliance rate, calculated as the proportion of patients who successfully comply with the limited cardiac monitoring strategy during treatment with trastuzumab based therapy (up to month 12), per protocol.. Participants who undergo a surveillance echocardiogram at month 6 and 12 within the protocol defined window (+/- 6 weeks) and no additional surveillance echocardiograms at any other timepoints will be considered compliant.
- Absolute change in LVEF during trastuzumab-based therapy (6 and 12 months after initiation of trastuzumab-based therapy)
- Absolute change in GLS during trastuzumab-based therapy (6 and 12 months after initiation of trastuzumab-based therapy)
- Incidence of trastuzumab interruption, defined by > 6 weeks between trastuzumab doses (>/= 1 dose missed).
- Incidence of asymptomatic LVEF decline, defined as an absolute decline of LVEF > 10% from baseline to below the lower limit of normal, or an absolute decline of LVEF > 15%.
- Total healthcare and cardiovascular-related health service utilization (MSK and non-MSK)

10.0 CRITERIA FOR REMOVAL FROM STUDY

Patients may withdraw from the study at any time and subsequently will follow routine cardiac monitoring per MSKCC guidelines. Reasons for study discontinuation at the discretion of the investigator include, but are not limited to:

- Change in patient eligibility
- Non-compliance with the defined protocol procedures
- Investigator's decision based on patient's best interest
- Withdrawal of consent
- Lost to follow-up
- Death

Patients who permanently discontinue trastuzumab (prior to month 12) for cardiac [e.g. symptomatic HF (NYHA class III/IV) or asymptomatic LVEF decline] reasons are evaluable for the primary endpoint but will be removed from the study intervention and undergo additional cardiac monitoring as clinically indicated per the treating physician. These patients will also undergo follow-up at 6 months post-end of treatment per section 7.0 and be included in the evaluation for the primary cardiac safety endpoint. Patients who are removed from study due to change in cancer treatment regimen (i.e. need to initiate anthracycline-based chemotherapy) or withdrawl of consent prior to receiving 1 dose of trastuzumab will not be evaluable for the primary cardiac safety endpoint and will be replaced. Patients who are removed from study for non-cardiac reasons (i.e. withdrawl of consent) and receive at least 1 dose of trastuzumab will be evaluable for the primary cardiac endpoint.

11.0 BIOSTATISTICS

The primary objective of this study is to determine the cardiac safety of a limited cardiac monitoring strategy in patients treated with a non-anthracycline trastuzumab-based regimen. Based on our preliminary work in a retrospective study of early stage HER2-positive patients treated with non-anthracycline trastuzumab-based regimens in clinical practice, the estimated rate of severe HF was 1.1% (upper limit 95% CI 4%).(30) Similarly, the rate of severe HF in the CLEOPATRA trial among patients with metastatic HER2-positive breast cancer treated with docetaxel plus trastuzumab plus placebo (TH) versus docetaxel plus trastuzumab plus pertuzumab (THP) was 1.8% and 1.0%, respectively.(36) The null hypothesis of this trial is that limited cardiac monitoring is not inferior to routine cardiac monitoring by a prespecified 2.9% margin in the severe HF event rate. This prespecified margin in terms of severe HF is based on the difference between the observed HF rate from our preliminary data of 1.1% and the upper bound of the 95% CI of 4%. This prespecified margin is also consistent with current clinical practice which is accepting of a HF risk of up to 4% among patients receiving trastuzumab-based therapy.

Descriptive and summary statistics will be used to report the total number of patients screened and to determine the rates and reasons for non-eligibility and patient refusal. All patients who received at least one dose of trastuzumab-based therapy will be considered evaluable for the primary cardiac safety endpoint, unless otherwise specified per section 10.0. Patients who are removed from the study should undergo routine cardiac monitoring as mandated by MSKCC guidelines. A modified intent-to-treat analysis will be carried out with inclusion of all evaluable patients. The proportion of patients with a severe HF event or CV death will be estimated together with an exact 95% confidence interval. An exact test will be used to test the null hypothesis H_0:

$P_{HF} \geq 0.04$ vs. the alternative H_1: $P_{HF} < 0.04$.(37,38) The null hypothesis will be rejected if no more than 3 participants develop a primary cardiac safety endpoint attributable to trastuzumab therapy.

The trial will be stopped if at any time 4 participants develop a primary cardiac safety endpoint attributable to trastuzumab therapy. If the trial stops early, the proportion of patients with heart failure will be estimated and a 95% confidence interval constructed from the negative binomial distribution.

Secondary endpoints:

Feasibility, as defined by the compliance rate of the limited cardiac monitoring strategy during trastuzumab therapy, will be estimated with 95% CI. Participants who undergo a surveillance echocardiogram at month 6 and 12 within the protocol defined window (+/- 6 weeks) and no additional surveillance echocardiograms at any other timepoints will be considered compliant. Changes from baseline to 6 and 12 months will be summarized descriptively for all secondary echocardiographic endpoints. LVEF and global longitudinal strain (both continuous measurements) will be further explored using linear mixed effects models modeling the measurements as a function of the visit (0, 6, and 12 months) and age at treatment initiation. The number of treatment interruptions and cases of asymptomatic LVEF decline will be tabulated across the different assessments. The cumulative incidences of treatment interruption and LVEF decline may be estimated with a non-parametric estimate together with 95% confidence intervals if there are a sufficient number of events ($n \geq 5$)

Information obtained from the medical record and reported in the HSUQ will be used to estimate total service utilization, utilization within categories (e.g., physician visits, ED/urgent care admissions, hospitalizations), and cardiac-related utilization, as well as total health care costs, cardiac-related health care costs, and out-of-pocket prescription drug costs borne directly by patients. All services provided at or by MSK will be identified in the EMR. Services provided outside of MSK will be identified from the HSUQ. In order to estimate costs, services identified in the medical record and through the HSUQ will be multiplied by unit cost values for each type of service. For most services, unit cost values will be assigned based on average Medicare reimbursement. For example, oncologist visits identified in the EMR and primary care visits reported in the HSUQ will be multiplied by the relevant unit cost values from the Medicare physician fee schedule. A hospitalization at MSK or outside of MSK will be valued at the average reimbursement for the specified DRG code, based on Medicare's prospective payment system (PPS) for hospital. Even though MSK is exempt from the PPS, the results of the study will have greater external validity if cost estimates reflect national average reimbursement and prices, rather than institution-specific costs, and this approach is well accepted in health care cost assessment. All health care costs will be reported in 2019 US dollars. Total and cardiovascular-related cost estimates will be adjusted for age and patient-specificfactors (e.g. cancer stage, cardiovascular risk factor profile) using multivariable regression analysis. Attribution of cardiace-related services will be based on the literature and investigator consensus.

Additional items in the HSUQ regarding health insurance, help with activities of daily living, household income, employment, and missed work/activity days will be analyzed and reported using descriptive statistics.

Sample size: In total, 190 evaluable females with HER2-positive breast cancer will be enrolled to achieve an evaluable at MSK. A sample size of 190 evaluable participants achieves 84% power to test for a non-inferiority proportion of 0.04 (no more than a 2.9% difference from the assumed current proportion) using a one-sided exact test with a significance level of 0.052. These results assume a baseline HF rate of 1.1% and were calculated using PASS software.(39) Accrual of the target sample size should be attainable within 3 years based on current estimates that 70 women with early breast cancer and 100 women with metastatic breast cancer are treated with non-anthracycline trastuzumab-based regimens at MSK per year.

Patients who are removed from study due to: (1) a change in cancer treatment regimen requiring anthracycline-based chemotherapy(i.e. need to initiate anthracycline-based chemotherapy), or (2) withdrawl of consent prior to receiving 1 dose of trastuzumab will not be evaluable for the primary cardiac safety endpoint and will be replaced. Patients who are removed from study for non-cardiac reasons (i.e. withdrawl of consent) and receive at least 1 dose of trastuzumab will be evaluable for the primary cardiac endpoint. To reach the appropriate sample size and targeted power in the study, patients who are not evaluable for the primary cardiac safety endpoint will be replaced. In total, approximately 194 patients will be enrolled to achieve an evaluable sample size of 190 patients.

12.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

12.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Inclusion/Exclusion Criteria. Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures. During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist. The individual signing the Eligibility Checklist is confirming whether or not the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

12.2 Randomization

Not applicable.

13.0 DATA MANAGEMENT ISSUES

A Research Study Assistant (RSA) will be assigned to this study, under the close supervision of the Clinical Research Supervisor and Clinical Research Manager in the Cardiology service. The responsibilities of the RSA will include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordination of the activities of the protocol study team.

The data collected for this study will be entered into a secure database on the MSK server. Source documentation will be available to support the computerized patient record. The principal investigator (Dr. Yu) will maintain ultimate responsibility for the clinical trial.

Data collected for this study will be entered into and managed via a secure REDCap Database. REDCap, Research Electronic Data Capture, is an open source platform that allows for the collection of research data in a secure manner over a web-based interface. Usage of the platform is contingent on an open source license. The platform was developed by Vanderbilt University which MSK has a standing agreement with to allow the usage of REDCap for academic/research purposes.

For this protocol, electronic data entry forms may be completed online by study staff. Electronic participant responses will also be collected either by sending participants a direct link or having the participants fill out the electronic survey on site.

Data will be housed in the Memorial Sloan Kettering Cancer Center's (MSKCC) New Jersey data center. REDCap has been approved by MSKCC's Information Security to store PHI. The MSKCC Information Systems group is responsible for applying all operating system patches and security updates to the REDCap servers. All connections to REDCap utilize encrypted (SSL-based) connections to ensure data is protected. The server is backed up nightly in the event that disaster recovery would be necessary, and system would need to be rolled back. Members of the Clinical Research Administration supporting the REDCap software will have access to REDCap projects for the purpose to ensuring the proper functioning of the database and the overall software system.

Permissions to the database for both internal and external users will be managed by the REDCap project manager or study staff. User access to the data is contingent on those a part of the study team and data sharing agreements in place with third party entities if applicable. Project managers are responsible for regularly auditing these permissions to ensure changes in staff are reflected appropriately.

REDCap has the ability maintain an audit trail of changes to the database providing a timestamp as well as the user making the update. In addition, a data resolution module offers the ability of opening and closing queries optionally requiring justification when data is being updated. Permission roles for data resolution are integrated in REDCap. Comprehensive system logs are also maintained of user activity and when changes to the database are made.

13.1 Quality Assurance

Monthly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action. The study team will meet regularly to review study progress and data integrity.

13.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled —Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials‖ which can be found at: http://www.cancer.gov/clinicaltrials/patientsafety/dsm-guidelines/page1

The DSM Plans at MSK were established and are monitored by the Office of Clinical Research. The MSK Data and Safety Monitoring Plans can be found on the MSK Intranet at: http://smskpsps9/dept/ocr/OCR%20Website%20Documents/Clinical%20Research%20Quality%20Assurance%20(CRQA)/MSKCC%20Data%20and%20Safety%20Monitoring%20Plan.pdf

There are several different mechanisms by which clinical trials are monitored for data safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: Data and Safety Monitoring Committee (DSMC) for Phase I and II clinical trials, and the Data and Safety Monitoring Board (DSMB) for Phase III clinical trials, report to the Center‘s Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for its level or risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industry sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

14.0 PROTECTION OF HUMAN SUBJECTS

Prior to the enrollment of each patient, the risks, benefits and objectives of the study will be reviewed with the participant, including a discussion of the possible toxicities and side effects. Alternative, non-protocol, treatment options will be discussed with the patient. It will be reviewed that participation in this clinical trial is voluntary and that the patient may withdraw consent at any time. The study is designed with careful safety monitoring for toxicity including physician visits and cardiac monitoring.

Potential Risks: Echocardiography is a safe and painless procedure and there are no known adverse effects from the ultrasound used for echocardiographic imaging. Some people may experience mild discomfort due to the pressure of the transducer on their chest during the study. A limited schedule of cardiac monitoring poses a potential risk that trastuzumab may be continued without interruption despite an asymptomatic LVEF decline. However, existing recommendations for routine cardiac monitoring lack evidence, and there is no data to show that routine cardiac monitoring performed every 3 months is associated with improved cardiovascular outcomes. The incidence of asymptomatic LVEF decline for non-anthracycline trastuzumab regimens is low (~3%) and our preliminary data suggests that continuous trastuzumab may be safe in patients with asymptomatic LVEF decline.[48] Furthermore, the median number of LVEF assessments performed in our prior retrospective study of HER2-positive breast cancer patients treated with paclitaxel and trastuzumab was 3 (range 1 to 5), indicating that outside of a clinical trial setting many providers are already following a strategy of limited cardiac monitoring. As an added safeguard against cardiotoxicity risk, participants will be followed closely for signs or symptoms suggestive of new onset HF or LVEF decline by study investigators, and additional cardiac imaging will be performed as clinically indicated. In the proposed cost analysis, there are no anticipated risks associated with self-administration of a healthcare resource utilization questionnaire.

Protection against risks: All participants will be treated with respect and sensitivity. Confidentiality will be maintained at all times during the study administration, and neither the patient's name nor other identifying information will be used for reports or publications resulting from this study. PIs and research coordinators will be available to answer questions and discuss findings with the participants or their health care provider. Screening procedures have been established to exclude individuals for whom a limited cardiac monitoring strategy is not appropriate or deemed unsafe. Our screening procedures begin with medical chart review to identify individuals with any condition or reasons that may prohibit study entry. Throughout the treatment period, all participants will be monitored closely every 3 months for signs or symptoms of heart failure, and symptom-triggered cardiac assessments will be performed at the discretion of the treating physician. For serious health problems (i.e. abnormal echocardiogram), a consultation with a MSK cardiologist will be expedited.

Potential Benefits: It is unlikely that the proposed study will provide any immediate benefit, either direct or indirect, to study subjects themselves but rather will benefit future cancer patients and, by extension, society in general by generating evidence to guide future development of appropriate-use cardiac monitoring guidelines during breast cancer therapy. It will be made clear to prospective subjects that no medical or other benefit is expected for them individually.

Costs/compensation: Patients will be charged for physician visits, routine laboratory tests and radiologic studies required for monitoring their condition. The participant is informed that there are no plans to provide financial compensation for any new products, tests, and discoveries that might come from this research.

Alternatives: The alternative to this study would be not to participate in the study and receive routine standard of care.

Confidentiality: Every effort will be made to maintain patient confidentiality. Research and hospital records are confidential. Patients' names and any other identifying information will not be used in reports or publications resulting from this study. Other authorized agencies and

appropriate internal personnel (e.g., qualified monitors from MSKCC) and external personnel, its authorized agents, the FDA, and/or other governmental agencies) may review patient records as required.

Monitoring of data to ensure safety: This study is to be monitored by the MSK IRB through continuing review/progress reports. These reports will be reviewed by the MSK IRB at a frequency deemed appropriate by the IRB.

Voluntariness of research participation: It is stated that taking part in this study is voluntary and patients have the right o withdraw at any time. Participation in the study will not impact on the clinical care patients receive.

Withdrawal: Participants will be made aware that they have the right to withdraw from participation in this trial at any time. Participants will be made aware of any changes that may impact their willingness to continue on study.

14.1 Privacy

MSK's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

The consent indicates that individualized de identified information collected for the purposes of this study may be shared with other qualified researchers. Only researchers who have received approval from MSK will be allowed to access this information which will not include protected health information, such as the participant's name, except for dates. It is also stated in the Research Authorization that their research data may be shared with other qualified researchers.

14.2 14.2 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered
an SAE.

SAE reporting is required as soon as the participant starts investigational treatment/intervention. SAE reporting is required for 30-days after the participant's last investigational treatment/intervention. Any event that occur after the 30-day period that is unexpected and at least possibly related to protocol treatment must be reported.

Please note: Any SAE that occurs prior to the start of investigational treatment/intervention and is related to a screening test or procedure (i.e., a screening biopsy) must be reported.

All SAEs must be submitted in PIMS. If an SAE requires submission to the HRPP office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be submitted within 5 calendar days of the event. All other SAEs must be submitted within 30 calendar days of the event.

The report should contain the following information:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment(s)
- If the AE was expected
- Detailed text that includes the following
    - An explanation of how the AE was handled
    - A description of the participant's condition
    - Indication if the participant remains on the study
- If an amendment will need to be made to the protocol and/or consent for
- If the SAE is an Unanticipated Problem

Only SAEs related (possible, probable, definite) to this study will be reported.

15.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.

3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

16.0 REFERENCES

1. Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A, McGuire WL. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. Science 1987;235:177-82.
2. Slamon DJ, Godolphin W, Jones LA et al. Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer. Science 1989;244:707-12.
3. Romond EH, Perez EA, Bryant J et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med 2005;353:1673-84.
4. Piccart-Gebhart MJ, Procter M, Leyland-Jones B et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med 2005;353:1659-72.
5. Slamon D, Eiermann W, Robert N et al. Adjuvant trastuzumab in HER2-positive breast cancer. N Engl J Med 2011;365:1273-83.
6. Cote GM, Sawyer DB, Chabner BA. ERBB2 inhibition and heart failure. N Engl J Med 2012;367:2150-3.
7. Tan-Chiu E, Yothers G, Romond E et al. Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel, with or without trastuzumab as adjuvant therapy in node-positive, human epidermal growth factor receptor 2-overexpressing breast cancer: NSABP B-31. J Clin Oncol 2005;23:7811-9.
8. Dang CT, Yu AF, Jones LW et al. Cardiac Surveillance Guidelines for Trastuzumab-Containing Therapy in Early-Stage Breast Cancer: Getting to the Heart of the Matter. J Clin Oncol 2016.
9. Genentech: Herceptin (trastuzumab): highlights of prescribing information, 04/2015 update. http://www.gene.com/download/pdf/herceptin_prescribing.pdf.
10. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Breast Cancer. Version 1. 2012. Available at www.nccn.org. Accessed June 30, 2015
11. Romond EH, Jeong JH, Rastogi P et al. Seven-year follow-up assessment of cardiac function in NSABP B-31, a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel (ACP) with ACP plus trastuzumab as

adjuvant therapy for patients with node-positive, human epidermal growth factor receptor 2-positive breast cancer. J Clin Oncol 2012;30:3792-9.
12. de Azambuja E, Procter MJ, van Veldhuisen DJ et al. Trastuzumab-Associated Cardiac Events at 8 Years of Median Follow-Up in the Herceptin Adjuvant Trial (BIG 1-01). J Clin Oncol 2014;32:2159-65.
13. Perez EA, Suman VJ, Davidson NE et al. Cardiac safety analysis of doxorubicin and cyclophosphamide followed by paclitaxel with or without trastuzumab in the North Central Cancer Treatment Group N9831 adjuvant breast cancer trial. J Clin Oncol 2008;26:1231-8.
14. Russell SD, Blackwell KL, Lawrence J et al. Independent adjudication of symptomatic heart failure with the use of doxorubicin and cyclophosphamide followed by trastuzumab adjuvant therapy: a combined review of cardiac data from the National Surgical Adjuvant breast and Bowel Project B-31 and the North Central Cancer Treatment Group N9831 clinical trials. J Clin Oncol 2010;28:3416-21.
15. Perez EA, Romond EH, Suman VJ et al. Trastuzumab Plus Adjuvant Chemotherapy for Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer: Planned Joint Analysis of Overall Survival From NSABP B-31 and NCCTG N9831. J Clin Oncol 2014;32:3744-52.
16. 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.
17. 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.
18. Bowles EJ, Wellman R, Feigelson HS et al. Risk of heart failure in breast cancer patients after anthracycline and trastuzumab treatment: a retrospective cohort study. J Natl Cancer Inst 2012;104:1293-305.
19. Chen J, Long JB, Hurria A, Owusu C, Steingart RM, Gross CP. Incidence of heart failure or cardiomyopathy after adjuvant trastuzumab therapy for breast cancer. J Am Coll Cardiol 2012;60:2504-12.
20. Jones SE, Savin MA, Holmes FA et al. Phase III trial comparing doxorubicin plus cyclophosphamide with docetaxel plus cyclophosphamide as adjuvant therapy for operable breast cancer. J Clin Oncol 2006;24:5381-7.
21. Tolaney SM, Barry WT, Dang CT et al. Adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer. N Engl J Med 2015;372:134-41.
22. Jones SE, Collea R, Paul D et al. Adjuvant docetaxel and cyclophosphamide plus trastuzumab in patients with HER2-amplified early stage breast cancer: a single-group, open-label, phase 2 study. Lancet Oncol 2013;14:1121-8.
23. Dang C, Guo H, Najita J et al. Cardiac Outcomes of Patients Receiving Adjuvant Weekly Paclitaxel and Trastuzumab for Node-Negative, ERBB2-Positive Breast Cancer. JAMA oncology 2016;2:29-36.
24. Yu AF, Mukku RB, Verma S et al. Cardiac safety of non-anthracycline trastuzumab-based therapy for HER2-positive breast cancer. Breast Cancer Res Treat 2017;166:241-247.
25. Giordano SH, Lin YL, Kuo YF, Hortobagyi GN, Goodwin JS. Decline in the use of anthracyclines for breast cancer. J Clin Oncol 2012;30:2232-9.

26. Thavendiranathan P, Grant AD, Negishi T, Plana JC, Popovic ZB, Marwick TH. Reproducibility of echocardiographic techniques for sequential assessment of left ventricular ejection fraction and volumes: application to patients undergoing cancer chemotherapy. J Am Coll Cardiol 2013;61:77-84.
27. Yu AF YN, Manrique CR, Thaler HT, Hudis CA, Dang CT, Steingart RM. (2013, November). Impact of Trastuzumab-Induced Cardiotoxicity and Subsequent Trastuzumab Interruption on Breast Cancer Outcome. Poster session presented at the meeting of the American Heart Association, Dallas, TX. .
28. Gong IY, Verma S, Yan AT et al. Long-term cardiovascular outcomes and overall survival of early-stage breast cancer patients with early discontinuation of trastuzumab: a population-based study. Breast Cancer Res Treat 2016;157:535-44.
29. Smith MD, Institute of Medicine (U.S.). Committee on the Learning Health Care System in America. Best care at lower cost : the path to continuously learning health care in America. Washington, D.C.: National Academies Press, 2012.
30. Mukku RB, Friedman M, Verma S, Liu J, Steingart RM, Hudis CA, Yu AF, Dang CT. Cardiac Safety of Trastuzumab without an Anthracycline in Patients with HER2-Positive Early Stage Breast Cancer: A Single Center Experience. Poster session presented at: San Antonio Breast Cancer Symposium; 2015 Dec 8-12; San Antonio, TX. .
31. Picard MH, Adams D, Bierig SM et al. American Society of Echocardiography recommendations for quality echocardiography laboratory operations. J Am Soc Echocardiogr 2011;24:1-10.
32. Leitman M, Lysyansky P, Sidenko S et al. Two-dimensional strain-a novel software for real-time quantitative echocardiographic assessment of myocardial function. J Am Soc Echocardiogr 2004;17:1021-9.
33. Centers for Medicare & Medicaid Services Web site. Accessed at www.cms.gov on 8 September 2015.
34. Lowrance W, Swartz C, Eastham J, Elkin E. The economic impact of robotic and open radical prostatectomy on patients and their families. J Urol 2014;191:e927-8.
35. Yancy CW, Jessup M, Bozkurt B et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;62:e147-239.
36. Swain SM, Ewer MS, Cortes J et al. Cardiac tolerability of pertuzumab plus trastuzumab plus docetaxel in patients with HER2-positive metastatic breast cancer in CLEOPATRA: a randomized, double-blind, placebo-controlled phase III study. Oncologist 2013;18:257-64.
37. Tunes da Silva G, Logan BR, Klein JP. Methods for equivalence and noninferiority testing. Biol Blood Marrow Transplant 2009;15:120-7.
38. NCSS, LLC. Non-Inferiority Tests for One Proportion. NCSS, LLC. Kaysville, Utah, USA. https://ncss-wpengine.netdna-ssl.com/wp-content/themes/ncss/pdf/Procedures/PASS/Non-Inferiority_Tests_for_One_Proportion.pdf.
39. PASS 14 Power Analysis and Sample Size Software (2015). NCSS, LLC. Kaysville, Utah, USA, https://ncss.com/software/pass.

17.0 APPENDICES

Appendix A: Cardiac questionnaire
Appendix B: Study Worksheet
Appendix C: Health Service Utilization Questionnaire
Appendix D: Cardiac Event Adjudication Form