NCI Protocol #:	**WF 01115**
WF Protocol #:	**01115**
IND # (If applicable):	
Protocol title:	**C**ommunity **H**ospital **I**dentification of High CV Risk Patients during Cancer Treatment (CHI)

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1 R43 HL 127878-01
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3U10CA081851-12
NCI/Division of Cancer Prevention
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Agent(s)/Supplier:

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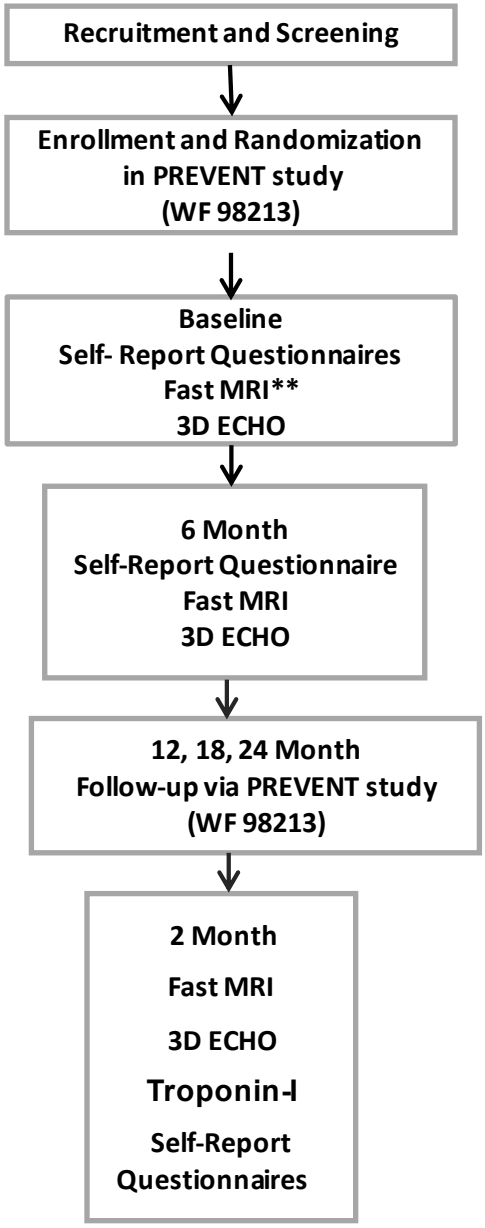
SCHEMA

Community **H**ospital **I**dentification of High CV Risk Patients during Cancer Treatment (CHI)



**** Must receive baseline MRI scan & 3-D ECHO**

Stratification Factors: Will be determined by the PREVENT study (WF 98213).

Study Sample: N=30

Study Duration: 6 months per subject

Brief Eligibility Criteria:

- Stage I-III breast cancer (including inflammatory and newly diagnosed recurrent breast cancer) or lymphoma Stage I-IV with a > 2 year life expectancy. Females and males are eligible to participate.
- Scheduled to receive chemotherapy with any anthracycline.
- ≥ 21 years of age
- Enrollment in WF 98213

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COVER PAGE

SCHEMA

1. OBJECTIVES

The overall of this proposal is to test in community hospitals the utility of a 10-min magnetic resonance imaging (MRI) scan protocol combined with proprietary image analysis algorithms for detecting early cardiovascular (CV) injury during receipt of chemotherapy for breast cancer (BrC) and lymphoma. This technology provides health-care delivery systems with a time-efficient method to identify those at risk of a future CV event so that prevention can be implemented to prolong survival and reduce morbidity in cancer survivors. Over 280,000 patients are diagnosed with BrC in the U.S. each year, and nearly 20% experience a serious, premature CV event.[i,ii,iii] In addition, each year 80,000 patients are diagnosed with Hodgkin's disease & non-Hodgkin's lymphoma who are also susceptible to CV injury based on their treatment regimens[iv,v,vi,vii,viii]. These CV events are the long-term consequences of acute cardiotoxic effects of the chemotherapy and could be prevented. Unfortunately, over 80% of BrC and lymphoma patients are treated in community hospitals that lack protocols to detect acute cardiotoxicity and intervene when the CV injury may be reversible **Albus' focus is to decrease CV related morbidity and improve the quality of life of BrC & lymphoma survivors by creating a strategy for detection, early risk stratification, and intervention for chemotherapy-related cardiotoxicity.**

While recent research indicates that conventional MRI, advanced echocardiography (global longitudinal strain and 3D) and serum biomarkers can detect CV injury early after receipt of Chemotherapy, these methods require lengthy and difficult examinations that are not routinely executed in community hospitals where the majority of patients with BrC & lymphoma are treated. Yet, 1-month deteriorations in traditional 45-min MRI measures are known to forecast 6-month subclinical deteriorations in left ventricular ejection fraction (LVEF) that are associated with CV events. At the same time, new observational data indicate therapy with HMG-CoA reductase inhibitors/statins administered early during receipt of Chemotherapy may prevent subsequent cardiac dysfunction and CV events. Our MRI fast scanning techniques remedy these community hospital implementation obstacles.

In this proposal, we propose to test the utility of these fast scans within an existing funded randomized clinical trial R01HL118740 of generic atorvastatin that is researching methods to prevent cardiotoxicity in patients treated with Chemotherapy for BrC and lymphoma (taking advantage of significant existing clinical trial resources). This study allows us to address our over-arching goal: to determine the optimal implementation (alone or in combination with other tests) of our proprietary MRI processes for forecasting CV injury in patients treated with Chemotherapy in community hospitals through performance of a Phase II comparative effectiveness study within an ongoing clinical trial.

Primary Objectives

Specific Aim 1: To determine if baseline to 2-month measures of left ventricular (LV) volumes, T1/T2 times, and/or aortic pulse wave velocity (all acquired within 10 minutes) can predict baseline to 6-month post Chemotherapy deteriorations in LVEF, as measured by a typical 45-min MRI.

Specific Aim 2: To compare the Albus 10-min MRI metrics with both ECHO (including PWV) and cardiac serum biomarkers (TnI) for predicting baseline to 6 month deteriorations in LVEF.

Specific Aim 3: To use exploratory algorithmic modeling to obtain optimal strategies for determining the combination of metrics (10-min MR, ECHO, serum biomarkers) at 2-months that predict the 6-month post Chemotherapy deteriorations in CV function.

To achieve these aims, we will study 30 subjects from community hospitals that also enroll in another study (funded through a NIH R01 mechanism) who are scheduled to receive Chemotherapy for Stage I-III BrC or lymphoma. Each participant will receive the new 10-minute Fast MRI, a conventional 45-min MRI (previously proven), a 3D ECHO/PWV, and cardiac serum biomarkers. The results of this pilot study will gauge the merit for funding a continued initiative to replace existing lengthy community hospital based scans with a rapid imaging solution. Ultimately, the desire is to expand this process to include those with heart failure, or other high CV risk profiles (e.g., hypertension, diabetes) to assess CV risk and direct therapy in community hospitals.

2. BACKGROUND

This study is significant in that it:

1) Creates a new, easy-to-implement, clinically viable process for community hospitals to identify the early evidence of CV injury throughout receipt of Chemotherapy for BrC & lymphoma that was previously only available in academic centers. This study will incorporate a 10-minute MRI scan (a dramatic reduction from the current 45-minute cardiac MRI procedures). Reduced acquisition times allow community hospitals to perform these new procedures with minimal disruption to existing clinical workflow. Our proposed study will be conducted in community hospitals, where >80% of patients currently receive treatment for breast cancer and lymphoma in the US. Therefore, the processes and procedures developed from this proposal will readily translate into clinical practice and be useful for the majority of US patients with BrC or lymphoma.
2) Allows identification of optimal combination of methods (MRI, ECHO) to detect myocardial injury upon receipt of chemotherapy. This will provide the ability to utilize data from these various modalities to develop and patent new predictive models that can direct the early detection of myocardial injury for the purpose of preventing future CV events in breast cancer and lymphoma survivors.
3) Directly compares the utility of our 10-min scan for those that are treated versus not treated with potentially cardioprotective therapy as they receive Chemotherapy.

2.1. Preliminary Data:

The research will be conducted by a highly experienced academic team. During the last 10 years, the assembled team has published 7 peer-reviewed manuscripts regarding the evolution of CV disease in individuals receiving chemotherapy.

2.1.1. Performance of a high-quality, 10-minute cardiac MR scan: Our 10-minute scan was developed to greatly reduce the scan time while maintaining the temporal resolution of the sequences so that strain analysis could be performed without a separate set of tagged scans. These goals were accomplished by utilizing higher parallel imaging acceleration factors, combining pairs of scans into single breath holds, and eliminating localizers for which other scans could be used. We have successfully refined and repeated the 10-minute protocol for acquiring data for LV volumes/ mass/ EF/ strain, T1/T2 mapping and aortic stiffness measures (Figure 1). The protocol is performed on widely available 1.5T scanners and is thus suitable for translation into community hospitals.

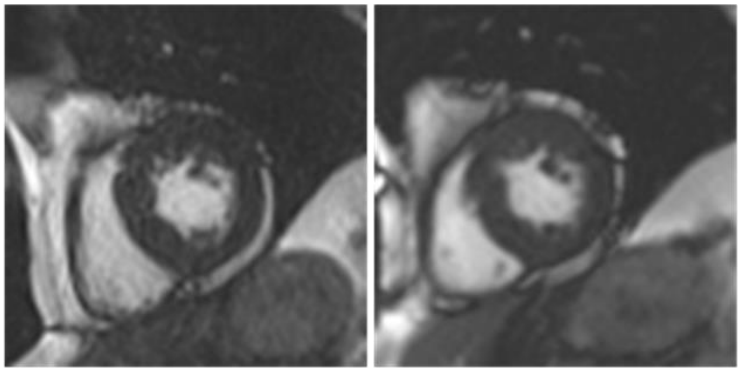


Figure 1. Middle short axis slices from fast 10-min scan (L) & Standard MR scan (R) have comparable spatial resolution (2x2mm), while the fast scan provides improved temporal resolution (28ms versus 44ms), permitting strain analysis with no need for a separate tagging acquisition.

2.1.2. Our MRI analytic measures of signal intensity within the left ventricle indicate myocellular injury in animals and are abnormal in patients receiving Chemotherapy.[ix,x] In animals and humans, we demonstrated that T1 changes identify myocellular injury that precede and forecast LVEF deterioration after Anthracyclines. We observed similar findings in a cohort of 63 human subjects followed longitudinally for 8 months. Our analytic methods allow segmentation of the LV myocardium, measurement of myocardial tissue characteristics indicative of injury and fibrosis, and then display this information in a format interpretable by physicians.

2.1.3. Atorvastatin attenuates declines in LVEF and is associated with few CV events after Chemotherapy. In a recent study of 40 patients scheduled to receive Anthracyclines, those randomized to receive atorvastatin (40 mg per day before and during Anthracyclines) had no decrease in LVEF at 6 months, but those randomized to receive Anthracyclines without statins had an 8% reduction in LVEF.[19] We observed fewer admissions for CHF among 628 breast cancer survivors receiving statins compared to those not prescribed a statin for secondary diagnosis of CVD.

2.1.4. Baseline to 1-month changes in LV performance during chemotherapy forecast future LVEF measures 6 months after initiating Anthracyclines. In 44 individuals receiving Anthracyclines, 25 experienced a 10% drop in LVEF at 6 months and the remaining 19 patients had a preserved LVEF (Figure 2). As shown, early imaging detects those that are/are not at risk for future CV events.

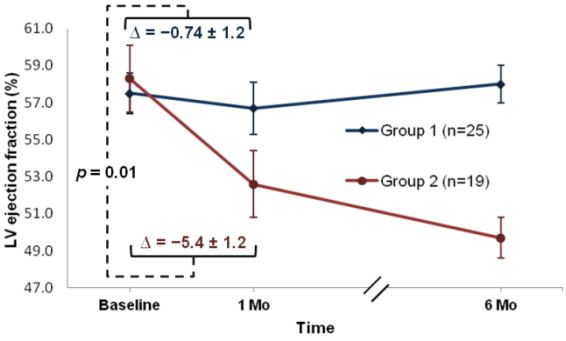
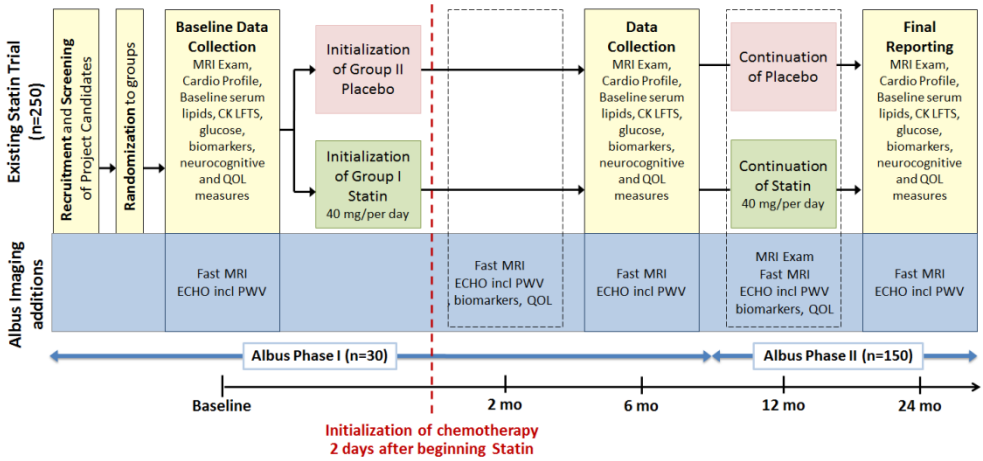


Figure 2. Change in left ventricular (LV) ejection fraction from baseline to 1 month during receipt of chemotherapy forecasts the change in LVEF from baseline to 6 months.

2.1.5. Within 3 months, Chemotherapy increases PWV, a predictor of CV events.[xi] In 40 individuals who received chemotherapy for BrC, lymphoma, or leukemia (and 13 age & sex-matched comparators), there was an increase PWV, which is a known independent predictor of adverse CV events. The magnitude of increase of PWV and aortic stiffness was equivalent to aging the CV system by 15–20 years.[xii]

3. SUMMARY OF STUDY PLAN

3.1 Study Design/Timeline and Integration with another Study: We propose to work with another double-blinded, placebo-controlled, randomized clinical trial of 250 patients = or > 21 years scheduled to receive Chemotherapy for Stage I-III BrC breast cancer or lymphoma, (R01-HL118740: 2/1/14-8/31/18) whose overall goal is to determine if statin administration reduces the 2-year incidence of LV dysfunction and early manifestations of heart failure.



The current study proposes a 10-min MRI scan, an ECHO, measures of serum troponin and other data captures at 2-months, as well as, a 10-min MRI scan and ECHO at 6-months (Figure 3). **The baseline to 2-month measurement period is selected to correspond to the clinical time point after the patient will have received Chemotherapy.**

3.2. The Wake Forest NCORP Research Base (WF NCORP RB) will recruit from NCORP sites with appropriate MRI facilities that treat modest numbers of breast cancer and lymphoma patients with anthracycline-based therapy. Importantly, the PI has visited and conducted interviews with all participating NCORP sites to verify their MRI, ECHO, and breast cancer and lymphoma recruitment capabilities.

4. PARTICIPANT SELECTION

4.1. Inclusion Criteria

4.1.1 Stage I-III breast cancer (including inflammatory and newly diagnosed recurrent breast cancer) or lymphoma Stage I-IV with a > 2 year life expectancy,

4.1.2 Scheduled to receive chemotherapy with an Anthracycline (doxorubicin or epirubicin)

4.1.3 ≥ 21 years of age

4.1.4 Prior cancers allowed if no evidence of disease

4.1.5 ECOG 0 or 1

4.1.6 Enrollment in NCI Protocol #: WF 98213. Patients must receive a 3D ECHO along with Baseline (98213) MRI prior to first chemotherapy treatment.

4.2 Exclusion Criteria

4.2.1 Patients with ferromagnetic cerebral aneurysm clips or other intraorbital/intracranial metal; pacemakers, defibrillators, functioning neurostimulator devices or other implanted electronic devices.

4.2.2 Most breast tissue expanders are not allowed. (If uncertain, inform the MRI tech to confirm eligibility status.)

4.2.3 Unable to provide informed consent

4.2.4 Symptomatic Claustrophobia

4.2.5 Pregnant or breasting feeding. Due to unknown risks and potential harm to the unborn fetus a negative serum pregnancy test must have been obtained per protocol 98213 in patients with child-bearing potential. For this reason patients of child-bearing potential must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence (not having sex), oral contraceptives, intrauterine device (IUD), DeProvera, tubal ligation, or vasectomy of the partner (with confirmed negative sperm counts) in a monogamous relationship (same partner). An acceptable, although less reliable method involves the careful use of condoms and spermicidal foam or gel and/or cervical cap or sponge prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her study physician immediately.

4.3. Inclusion of Patients and Minorities

Table 2: Race/Ethnicity

Gender	White	Black or African-American	Hispanic or Latino	Asian or Pacific Islander	Unknown	Total
Male	3	1	0	0	0	4
Female	21	4	1	0	0	26
Total	24	5	1	0	0	30

4.4. Recruitment and Retention Plan

4.4.1 Over 300 breast and lymphoma patients should be eligible for enrollment among the NCORP sites, approximately 14% of whom will be males. Assuming conservatively that 17% (1 in 6) of the patients will consent to the study, we expect ~50 patients *could be* enrolled once the study is active at all planned sites. If enrollment is unexpectedly low, we can add additional NCORP sites in which study coordinators, imaging expertise, and patient populations are readily available.

4.4.2. At each site, specific recruitment plans may include the following according to the site's institutional policy: screening clinic charts; tumor registry data; referral sources such as patient advocate groups, retirement communities, churches, support organizations, community organizations, newspapers, radio; or patient recruitment posters and recruitment letters.

4.4.3. The research PI or designee at each WF NCORP Research Base NCORP, which may include the clinic physician, resident, research nurse or research assistant, will review cancer registry and medical chart information to identify patients eligible for this protocol. Patients identified using these methods will be asked to join the study during their next clinic visit/consultation.

Accrual is expected to be 5 patients per month. Targeted accrual should be met in approximately 8 months for the study. A maximum of 30 patients will be enrolled on this trial. Patients will be followed for 6 months as part of this study.

5. AGENT ADMINISTRATION

5.1. A sedative may be administered to claustrophobic patients.

6. PHARMACEUTICAL INFORMATION

6.1 Sedative

In the event a patient is claustrophobic (extreme discomfort or fear of small spaces) they may be offered an intravenous injection of a sedative medication to make the patient drowsy, relaxed and comfortable during the MRI scan. Because sedatives may decrease alertness and cause lightheadedness or dizziness, the patient must have another adult drive them home from the clinic if they are given a sedative.

Possible risks and side effects of the sedative include:

Most Common Events may occur in about 2% of patients.

- dizziness
- headache

Less Common

- unusually fast/slow/irregular heartbeat,
- fainting,
- confusion,
- mental/mood changes,
- trouble breathing,
- muscle twitching and involuntary movements,

Rare but Serious Events

- throat discomfort,
- skin rash and hives.

6.2 Agent Accountability

Each participating MRI NCORP site will maintain a careful record of the inventory and disposition of the sedative according to institutional policy.

7. CLINICAL EVALUATIONS AND PROCEDURES

Note: *Fast MRI is embedded in (98213) Baseline and 6 month MRI. Data will be extracted for use in this protocol. Only additional Fast MRI is at 2 months and additional 3D ECHO will be required at 2 and 6 months.*

7.1 Schedule of Events

At each participating Research Base site, medical charts will be screened to determine potential eligibility by physicians (including residents or fellows, if applicable), research nurses, or clinical research associates. This information should be recorded on the Screening Form. Patients identified as potentially eligible will then be asked to consider joining the study. Patients meeting initial eligibility criteria and who agree to participate in the study will sign informed consent. Baseline Fast MRI & 3D ECHOs will be captured in tandem with baseline PREVENT study MRI. The acquisition of the patient's clinical ECHO at baseline can be used for the CHI study so that duplication of this measurement is not required. Patients will be asked to complete the Self-Report Questionnaires.: At 2 months a Fast MRI, 3D ECHO, ultrasensitive Troponin I and Self-Report Questionnaires will be obtained. At 6 months a Fast MRI & 3D ECHO will be captured in tandem with PREVENT study MRI and Self-Report Questionnaires will be obtained.

7.2. Baseline Evaluations

MRI Variables -
The primary cardiac and vascular outcome measures include LVEF and PWV. LVEF was selected as our primary cardiac outcome because clinically it has been used for >30 years to guide the administration of potentially cardiotoxic chemotherapy.[xiii,xiv] Also, we will measure LV end diastolic volume, LV end systolic volume, myocardial strain and strain rate, and mass according to published standards and treat them as continuous variables.[xv,xvi,xvii] Since vascular stiffness is associated with CV events,[xviii] we will measure PWV because it measures aortic stiffness without reliance on measures of central aortic pressure, is highly reproducible, and it can be very accurately measured with MRI because it does not require external marking of central landmarks.[xix,xx,xxi] Finally, we will acquire T1 and T2 maps of the LV myocardium that have been shown in other studies to be associated with myocardial injury.[xxii,xxiii] The fast MRI protocol is short (10 mins.). All MRI scans will be performed after a formal evaluation of the physical performance parameters of the CMR scanner, completed daily using standard manufacturer-recommended evaluation methods with calibration phantoms to ensure consistent measures over time. Each MRI assessment will be blinded to patient identifiers, the corresponding MRI exam, and prior MRI exams of the same measure (a blinded, unpaired read). A complete double reading on 15% of the CMR cases will be performed for quality control. All study participants will be offered benzodiazepines to assist in easing any claustrophobia concerns.

ECHO Variables - A standardized ECHO-Doppler examination with 2D and 3D ultrasound and spectral Doppler will be performed according to American Society of Echocardiography (ASE) guidelines[xxiv,xxv,xxvi] and as previously described by Dr. Kitzman and colleagues in multiple clinical trials.[xxvii,xxviii,xxix,xxx] The exam will be focused on evaluation of LV volumes and EF (in 2 and 3D), mass, global longitudinal strain (GLS), diastolic function, and pulse wave velocity and is designed to produce variables of interest to patients with BrC & lymphoma and to match key variables from the cardiac MRI exams. All field sites have current model Philips iE33 instruments, enabling standardized, uniform, efficient acquisition of all variables in a single exam. Exams will be performed by registered cardiac diagnostic sonographers. Analysis: For 2D LV volumes, endocardial borders will be traced in end-diastolic and end-systole in the apical 4 and 2 chamber views and calculated by the modified Simpson's technique. 3D echo has the potential for more accurate LV volumes and EF because it uses all voxels in the acquired 3D, full-volume dataset and is relatively independent of geometric assumptions. Global 3D LV volumes will be analyzed with semi-automated border detection over full cardiac cycles using Q-lab (Philips) software. LVEF will be calculated by the standard formula. Circumferential and longitudinal strain will be measured from the short axis and apical views, respectively. Doppler mitral flow and annular displacement (septal and lateral) velocities will be traced from the apical 4 chamber view for peak early, atrial, and systolic velocities, early deceleration time, and arterial PWV will be assessed from carotid and femoral pulse Doppler, ECG, and measured distance.[xxxi] All measures will be performed in triplicate. Overall image quality will also be graded as good, fair, poor, unevaluable.

Quality of Life
Self-Report Questionnaires:
The Self-Reported questionnaires are a collection of well-validated, brief, fee-free instruments assessing key patient reported outcomes related to this study. For this study, we will include the short forms for quality of life. The total administration time for these questionnaires is 5 minutes.

7.3. Evaluations During Study Intervention

Self-Report questionnaires will be obtained at 2 months

As part of this study, an additional measurement of ultrasensitive Troponin I will be collected at 2-months, as well as, a Fast MRI and 3D ECHO.

7.4. Evaluations at Completion of Study Intervention

At 6-months, all study participants will complete Self-Report questionnaires, have a Fast MRI and 3D ECHO.

7.5. Post-intervention Follow-up Period. N/A

7.6 Methods for Clinical Procedures

Processes for obtaining the Self-Report questionnaires, fast MRI, and ECHO are provided in the Appendices.

Fast MRI & 3D ECHO invoices should be emailed to Albus Imaging at clinicaltrials@albusimaging.com or mailed 116 Lowes Food Drive, Suite 217, Lewisville, NC 27023 (Email is preferred.)

7.7. Study Parameters Table

Enrollment in PREVENT study should be documented. Fast MRI is embedded in (98213) Baseline and 6 month MRI. Data will be extracted for use in this protocol. PREVENT study data will be made available to the CHI research team.

Evaluation Procedure	Baseline	2 Months	6 Months	Description
Informed Consent	X			
Fast MRI (A)	X	X	X	LV Volumes (incl LV end diastolic volume, LV end systolic volumes), Pulse Wave Velocity, myocardial strain & strain rate, mass, T1 and T2 maps.
Fast MRI Encounter Form	X	X	X	
3D ECHO (A)	X	X	X	LV Volumes, Ejection Fraction (in 2 and 3D), mass, global longitudinal strain (GLS), diastolic function, and pulse wave velocity.
ECHO Encounter Form	X	X	X	
Lab – ultrasensitive Troponin-I		X		
Self-Report Questionnaires	X	X	X	
Flow Sheet/ Addenda	X	X	X	
Toxicity Assessment Sheet (TAS)				If applicable any time during study.
Early Withdrawal Treatment/Consent		Submit this form when a participant withdraws from active treatment or withdraws consent prior to study completion.		
Screening Form		Submit this form every month.		

(A) Must be obtained prior to first chemotherapy treatment

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7.8. Off Treatment Criteria

Participants may stop participating for the following reasons: adverse event or serious adverse event, concomitant medications, medical contraindication, or interruption of chemotherapy due to adverse events or death.

Participants will continue to be followed, if possible, for safety reasons and in order to collect endpoint data according to the schedule of events. The study is designed to account for dropouts due to poor health or death; thus, there will be no replacement of subjects that must drop out of the study after enrollment.

Patients who are unable to have an MRI or ECHO at baseline will not be allowed to continue participation in the study.

7.9 Off-Study Criteria

Participants may go 'off-study' for the following reasons: the protocol intervention and any protocol-required follow-up period is completed, adverse event/serious adverse event, lost to follow-up, concomitant medication, medical contraindication, withdraw consent, or death.

8. PROTOCOL SPECIFIC TRAINING REQUIREMENTS

8.1 MRI Training

- The study PI presented the MRI protocol for review and discussion with the MRI technologists and associated study coordinators during the Investigator meeting held at the 2013, 2014 and 2015 Annual Research Base NCORP Meeting.

  Prior to the start of participant enrollment into the study, Wake Forest University Medical Center cardiology imaging specialists observe and continue MRI training at each of the study locations.

  Each site will be required to submit two satisfactorily performed studies to the image coordinating center at Wake Forest before initiating the study per protocol 98213 requirements.

8.2 ECHO Training

- For ECHOs, the field site sonographers will be trained in the study protocol by the Wake Forest Echo Core Lab Director (Dr. Kitzman) and chief sonographer (Ms. Stewart, RDMS) prior to study launch using written, illustrated sonographer instructions, a teaching video, didactic sessions, practice patients, field site visits, and 2 final qualifying test cases.

9. SPECIMEN MANAGEMENT

9.1 Lab Corp: Troponin-I at 2 months

Lab Corp will be utilized for all labs. LabCorp couriers will deploy to each site from local LabCorp facilities for specimen pick-up as samples are drawn. All specimens should be collected in containers provided by LabCorp. Note storage times and temperature instructions for each test.

9.2 Collection and Handling Procedures

Refer to Appendix Lab Instructions.

10. REPORTING ADVERSE EVENTS

- A list of adverse events/serious adverse events that have occurred or might occur that are related to this study intervention can be found in Section 6.2.
- Adverse Event/Serious Adverse Event reporting begins after the informed consent is signed.
- Serious Adverse Events occurring within 30 days of study completion must be reported via FDA Form 3500 (MedWatch).

10.1 Protocol Specific Reporting for Adverse Events (AEs)

- DEFINITION: An adverse event (AE) is any untoward medical occurrence in a study participant.

- **Grades 1, 2, and 3 expected (solicited) and unexpected (unsolicited) AEs that meet the above definition for an AE and are ONLY definitely related, possibly related or probably related to this study intervention should be reported to the RB DMC using the Toxicity Assessment Sheet.**

10.2 Protocol Specific Reporting for Serious Adverse Events (SAEs)

DEFINITION: ICH Guideline E2A and Fed. Reg. 62, Oct. 7, 1997 define serious adverse events as those events that meet any of the following criteria?

- Results in death
- Is life threatening (Note: the term life threatening refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe).
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Is a congenital abnormality/birth defect.
- Events that may not meet these criteria, but which the investigator finds very unusual and/or potentially serious, will also be reported in the same manner.
- **Grades 3, 4, and 5 expected (solicited) and unexpected (unsolicited) SAEs that meet the above definition for SAEs and/or regardless of attribution (i.e. regardless of whether they are related to this study intervention or not) should be reported to the RB DMC using the FDA Form 3500 (MedWatch).**
- Site staff and/or Principal Investigators will report to the RB Data Management Staff within 24 hours of discovering the details of all unexpected severe, life threatening (grade 4) and/or fatal adverse events (grade 5) if there is reasonable suspicion that the event was definitely, probably, or possibly related to the study intervention.

  Otherwise, the MedWatch should be sent to the NCORPRB DMC by fax or email within 10 working days of discovering the details of the SAE.

Hospitalizations that are scheduled for routine treatments and procedures unrelated to study intervention do not need to be reported.

Data Elements to include on the MedWatch are:

- SAE reported date
- CTCAE Term (v4.03)
- Event onset date and event ended date
- Severity grade (use table provided in Section 10.1.3 below)
- Attribution to study intervention (relatedness)
- Action taken with the study participant and intervention
- Outcome of the event
- Comments

10.3 Guidelines to determine grade and severity of AEs and/or SAEs

Identify the adverse event using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The CTCAE provides descriptive terminology and a grading scale for each adverse event listed. A copy of the CTCAE can be found at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40

AEs will be assessed according to the CTCAE grade associated with the AE term. AEs that do not have a corresponding CTCAE term will be assessed according to the general guidelines for grading used in the CTCAE v4.03. as stated below.

Grade	Severity	Description
1	Mild	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
3	Severe	Severe or medically significant but not immediately life-threatening; Hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
4	Life threatening	Life-threatening consequences; urgent intervention indicated.
5	Fatal	Death related to AE.

Activities of Daily Living (ADL)

* Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

** Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

The Research Base Grant PI, Safety and Toxicity Review Committee and/or Study Chair will take appropriate action to inform the membership and statistical personnel of any protocol modifications and/or precautionary measures, if this is warranted.

The RB DMC is responsible for communicating AEs/SAEs to the FDA, WF IRB, the WF Safety and Toxicity Review Committee (STRC) and/or other regulatory agencies as appropriate per agency reporting requirements.

Institutions must comply with their individual Institutional Review Board (IRB) policy regarding submission of documentation of adverse events. All MedWatch reports should be sent to the local IRB in accordance with the local IRB policies.

10.4 Follow-up of SAEs

Site staff should send follow-up reports as requested when additional information is available. Additional information should be entered on the MedWatch form in the appropriate format. Follow-up information should be sent to the RB Data Management Center as soon as available.

SAEs (Grade 4 and/or Grade 5) for this protocol should be followed for those related to the study intervention. Documentation should include:

- PID
- Date of SAE
- Description of the event
- Relationship of the SAE to the study intervention
- Severity
- Intervention/Resolution

11. STUDY MONITORING

11.1 Data Management Schedule

The Eligibility checklist/Registration Form should be completed on-line prior to placing the patient on study. Data forms will be submitted to the WF NCORP Research Base. Mail to Suite 101 2000 W. 1st Street Winston-Salem, NC 27104 or fax to (336) 713-6476 according to the timetable below:

Form	Submission Schedule
Consent Form, Flow Sheet/Addenda, Fast MRI Encounter Form, ECHO Encounter Form, Self- Report Questionnaires	Baseline – within 14 days of registration
Self-Report Questionnaires	Baseline (+ or - 14 days)
Fast MRI Encounter Form, ECHO Encounter Form, 2-month Self Reporting Questionnaires Flow Sheet/ Addenda, TAS if applicable, Lab – Troponin-1	2 months (+ or - 14 days)
Fast MRI Encounter Form, ECHO Encounter Form, Self-Reporting Questionnaires, Flow Sheet/Addenda	6 months (+ or - 14 days)
Early Withdrawal Form	Participants who withdraw from treatment **or** study prior to completion. Submit at withdraw.
Screening Form	Every month

11.2 Case Report Forms

Participant data will be collected using protocol-specific case report forms (CRF).

11.3 Source Documents

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

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

- Clearly labeled in accordance with HIPAA practices so that they can be associated with a particular participant or PID;
- Legibly written in ink;
- Signed and dated in a real time basis by health care practitioner evaluating or treating the participant;
- Correction liquid or tape must not be used in source documents or on CRFs.
- Corrections are made by drawing a single line through the error. Do not obliterate the original entry. Insert the correct information, initial, and date the entry.

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

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

11.4 Data and Safety Monitoring Board

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

11.5 Record retention

Clinical records for all participants, including CRFs, all source documentation (containing evidence to study eligibility, history and physical findings, laboratory data, results of consultations, etc.), as well as IRB records and other regulatory documentation will be retained by the Investigator in a secure storage facility in compliance with HIPAA, OHRP, FDA regulations and guidance, and NCI/DCP requirements unless the standard at the site is more stringent.

11.6 CDUS Reporting

The WF NCORP Research Base Data Management Center will submit quarterly reports to DCP/CTEP by electronic means using the Clinical Data Update System (CDUS)

12. STATISTICAL CONSIDERATIONS

12.1. Study Design/Endpoints

We propose to test the utility of fast MRI scans to identify cardiotoxicity in patients treated with Chemotherapy for BrC or Lymphoma (taking advantage of existing clinical trial resources). This study allows us to address our over-arching goal: to determine the optimal implementation (alone or in combination with other tests) of our fast MRI processes for forecasting CV injury in patients treated with Chemotherapy in community hospitals through performance of a Phase II comparative effectiveness study within an ongoing clinical trial.

Primary endpoints include LVESV, LV end diastolic volume (LVEDV), LV mid-wall circumferential strain, T1 & T2 Mapping, PWV, aortic wall thickness compared between fast MRI & ECHO and Troponins.

12.2. Primary Aims

Specific Aim 1: To determine if baseline to 2-month measures of left ventricular (LV) volumes, T1/T2 times, and/or aortic pulse wave velocity (all acquired within 10 minutes) can predict baseline to 6-month post Chemotherapy deteriorations in LVEF, as measured by a typical 45-min MRI.

Specific Aim 2: To compare the 10-min MRI metrics with both ECHO including PWV and cardiac serum biomarker (TnI) for predicting baseline to 6 month deteriorations in LVEF.

Specific Aim 3: To use exploratory algorithmic modeling to obtain optimal strategies for determining the combination of metrics (10-min MRI, ECHO, serum biomarkers) at 2-months that predict the 6-month post Chemotherapy deteriorations in CV function.

12.3. Analysis Plan

Aim 1: We will estimate the correlations between the baseline to 2-month changes in 3 measures from the 10-min MRI (LV volumes, T1/T2 times and aortic PWV) and the baseline to 6-month changes in LVEF as measured by a 45- min MRI. With 30 patients available, we will have 80% power to detect a correlation of 0.5 between each of the baseline to 2-month changes in 10-min MRI measures with the baseline to 6-month change in LVEF. To examine whether the variability of the two MRI assessments (10-min and 45-min) is comparable we will calculate variance ratios for different CV measures and determine their comparability (i.e., they will be considered comparable if they fall between 0.8 and 1.2).

Aim 2: The second Aim will focus on determining the association between early changes in our 10-min MRI as well as changes in conventional measures of CV dysfunction including: 45-min MRI, ECHO (including PWV) and cardiac serum biomarker (TnI) at 2-months and 6-month deteriorations in LVEF. In 2 fashions, we will estimate the change in each of the novel and conventional measures after 2-months and determine how well they predict the baseline to 6-month change in LVEF. First, we will estimate the correlation between the baseline to 2-month changes for each measure with the baseline to 6-month change in LVEF. Also, we may fit linear regression models to estimate the relationship of these early changes in measures with the 6-month change in LVEF adjusting for patient level characteristics. Next, we will dichotomize the patients into those who exhibit a drop in LVEF from baseline to 6 months (absolute level of EF below 50% or a 10% or greater drop in LVEF) and those who don't. We will then perform a series of 2 sample t-tests to see whether the mean change after 2 months in LVEF and the other measures is different for patients who exhibit a drop in LVEF at 6 months.

Aim 3: We will fit a series of exploratory multiple logistic regression models where the outcome measure will be the binary variable LVEF drop baseline to 6-months (yes/no) and each model will begin with a key predictor (10-min MRI measures, 45-min MRI measure or ECHO measure) and then we will add in additional clinical and patient level characteristics into the models to determine whether there is a combination of clinical and demographic characteristics that enhance the prediction of LVEF drop for each measure of CV dysfunction. ***We recognize that with a limited sample size these models will provide initial information about variables that may be useful in predicting the outcome of interest.*** In addition, we will consider using alternative model building strategies such as artificial neural network (ANN) in order to determine whether there are combinations of the measures taken at baseline and 2-months that predict a drop in LVEF at 6 months. For these analyses we will have over 80% power to detect correlations of 0.50 between the baseline to 2-month changes in each measure and the baseline to 6 month changes in the outcomes assuming a 2-sided test with alpha=0.05 and 30 patients. In addition, we will have 80% power to detect a difference between groups (those with a 6-month drop in LVEF vs those without a 6-month drop) equal to 1.06 standard deviations for the measure of interest assuming a 2-sided test with alpha=0.05 if roughly half of the patients exhibit a drop in LVEF after 6 months. If only 33% (n=10) exhibit a drop at 6-months then we will have 80% power to detect a difference of 1.12 standard deviations. The primary goal of this Aim for this study is to determine which measures exhibit a correlation with the 6-month outcome and show some predictive strength in the logistic regression models. Those measures that meet these criteria will then be considered in Phase II, which will allow us to directly compare the predictive strength of each measure with each other. In Phase II, when our sample size will increase to 150 patients, we will be able to fit more robust statistical models to develop predictive equations for identifying patients at risk for a drop in LVEF based on their initial and 2-month measures. With the larger sample size we will have over 80% power to detect correlations between the predictors and 6-month change in LVEF of 0.23 or larger. In addition, we will be able to mean differences in patients with or without a 6-month drop in LVEF of less than 0.58 standard deviations if at least 20% (n=30 out of 150) of the patients exhibit a 6-month drop in LVEF.

12.4. Secondary Analyses:

Additional cost analyses will be performed. Costs for outpatient services will be based on the Outpatient Prospective Payment amounts (nationwide and specific locality) based on Healthcare Common Procedure Codes or Ambulatory Payment Classification groups.[xxxii] MRI or ECHO will be converted into cost using the Medicare charges. [xxxiii] *Direct Medical Costs:* Medicare diagnosis-related group reimbursement rates will be applied to define hospital costs (nationwide - and area-specific) using the PC Pricer Prospective Payment System estimator. Total procedural times including preparation and recovery time will also be obtained. Other cost data we will analyze includes: procedural complications cost, inflation/discounting, and societal perspectives.[xxxiv] *Cumulative Costs*: Costs will be aggregated by combining direct medical and indirect costs with complication and incidental finding costs to provide a summed follow-up cost for each study participant.

12.5. Power and Sample Size considerations for the primary hypothesis

This is pilot trial of 30 subjects. Because of the budget limits of a pilot trial, we did not choose the sample size specifically to detect a 0.5 correlation – but felt that this was a reasonable sample size and with that sample size we could detect a correlation of 0.5. We aim to determine which measures exhibit a correlation and which also show some predictive strength in the logistic regression models. We will use this for the design of our Phase II study which will show the predictive strength of each measure and will be sufficiently powered.

12.6. Evaluation of Toxicity

All participants will be evaluable for toxicity from the time of their first MRI.

12.7. Interim Analysis

Interim reviews will be performed by the Data Safety Monitoring Committee every six months to assess accrual, retention, compliance, the incidence of AEs, SAEs, diabetes and LV function measures.

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