Protocol Title:	PROactive evaluation of function to Avoid CardioToxicity (PROACT)
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PROACT
PROactive evaluation of function to Avoid CardioToxicity

Washington University School of Medicine
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Protocol: VAL-1020P(A)
Version: 6.0
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Lauren Baldassarre, MD, FACC, FSCMR, FSCCT	Yale	Cardiology
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Data and Safety Monitoring Committee:	**Institution:**	**Modality:**
Edward Geltman, MD	Washington University	Cardiology
Nusayba Bagegni, MD	Washington University	Medical Oncology
Elena Deych	Washington University	Cardiology Statistician

This protocol was co-written by Daniel J. Lenihan, MD, FACC and Susan F. Dent, MD, FRCPC, Medical Oncologist at Ottawa Hospital Cancer Center.

PROACT
PROactive evaluation of function to Avoid CardioToxicity

Protocol Revision History

Initial Approval Version 08/24/2018

Amendment 1: Version 2.0 05/13/2019

Summary of Changes	
Protocol v1.0	**Protocol v2.0**
	Page 1 **Co-Investigators** Addition of the following co-investigators: Keith Stockerl-Goldstein, MD Shahed Badiyan, MD Clifford Robinson, MD
Page 8 **1.3 Study Design** Original: Breast cancer, lymphoma, and sarcoma patients scheduled to receive anti-cancer therapy, who are previously enrolled in the SURVIVE Registry, will be screened for study participation.	**Page 8** **1.3 Study Design** Modified: Breast cancer, lymphoma, ~~and~~ sarcoma, leukemia, myeloma, and lung cancer patients scheduled to receive anti-cancer therapy, who are previously enrolled in the SURVIVE Registry, will be screened for study participation.
Page 8 **1.6 Inclusion Criteria** Original: 3) Histological diagnosis of early or metastatic breast cancer, lymphoma, or sarcoma (patients with treated and clinically stable brain metastasis are acceptable)	**Page 8** **1.6 Inclusion Criteria** Modified: 3) Histological diagnosis of early or metastatic breast cancer, lymphoma, ~~or~~ sarcoma, leukemia, myeloma, or lung cancer (patients with treated and clinically stable brain metastasis are acceptable)
Page 17 **5.1 Summary Protocol** Original: Breast cancer, lymphoma, or sarcoma patients scheduled to receive anti-cancer therapy with or without concomitant radiotherapy and enrolled in the SURVIVE Registry will be evaluated based on baseline MyoStrain® segmental dysfunction risk profile.	**Page 17** **5.1 Summary Protocol** Modified: Breast cancer, lymphoma, ~~or~~ sarcoma, leukemia, myeloma, or lung cancer patients scheduled to receive anti-cancer therapy with or without concomitant radiotherapy and enrolled in the SURVIVE Registry will be evaluated based on baseline MyoStrain® segmental dysfunction risk profile.
	Page 18 **Figure 2 – Study Flow Diagram** Modified to reflect addition of leukemia, myeloma, and lung cancer and to update the secondary inclusion criteria as listed in the context of the protocol.
Page 20 **5.3 Study Population** Original: Subjects enrolled in the SURVIVE Registry and scheduled to undergo chemotherapy or targeting treatment as well as clinically indicated cardiac MRI will be will be consented for possible inclusion in PROACT.	**Page 20** **5.3 Study Population** Modified: Subjects enrolled in the SURVIVE Registry and scheduled to undergo chemotherapy or targeted~~ing~~ treatment ~~as well as clinically indicated cardiac MRI will be~~ will be consented for possible inclusion in PROACT.
Page 20 **5.4 Inclusion Criteria** Original: 3) Histological diagnosis of early or metastatic breast cancer, lymphoma, or sarcoma (patients with treated and clinically stable brain metastasis are acceptable)	**Page 20** **5.4 Inclusion Criteria** Modified: 3) Histological diagnosis of early or metastatic breast cancer, lymphoma, ~~or~~ sarcoma, leukemia, myeloma, or lung cancer (patients with treated and clinically stable brain metastasis are acceptable)

Amendment 2: Version 3.0 09/05/2019

Summary of Changes	
Protocol v2.0	**Protocol v3.0**
Page 17 **5.1 Summary Protocol** Original: Eligible patients will be randomized 1:1 into the MyoStrain® guided treatment arm versus the Myostrain® blinded observational arm, as shown in Figure 2. The treatment arm will guide patient management by augmenting standard of care with serial MyoStrain® monitoring of the impact of cancer therapy on myocardial function. The observational arm will provide investigators with LVEF and LVEDV/LVESV measurements, which are clinical. The standard of care assessments by cardiac MRI, will not include MyoStrain® assessments.	**Page 17** **5.1 Summary Protocol** Modified: Eligible patients will then be randomized 1:1 into the MyoStrain® guided treatment arm versus the Myostrain® blinded observational arm, as shown in Figure 2. The treatment arm will guide patient management by augmenting standard of care with serial MyoStrain® monitoring of the impact of cancer therapy on myocardial function by providing physicians with MyoStrain® values, in addition to LVEF, LVEDV, and LVESV. In t~~T~~he observational arm, physicians will only be provided ~~investigators~~ with LVEF, LVEDV, and ~~/~~LVESV, which are clinical measurements. The standard of care assessments by cardiac MRI, will not include MyoStrain® assessments.

	Page 17 **5.1 Summary Protocol** Added: In order to obtain the MyoStrain® values, MRI images obtained will be uploaded de-identified to Myocardial Solutions, Inc. After the baseline scan, Myocardial Solutions, Inc. will inform research staff whether the patient met criteria for continued follow up in the study. At that time, the patient will be randomized to one of the two arms, as previously described, and Myocardial Solutions, Inc. will be made aware of the randomization result. If randomized to the blinded observational arm, no results from any cardiac MRI obtained for the study will be provided to physicians from Myocardial Solutions, Inc. If randomized to the MyoStrain® guided treatment arm, MyoStrain® results and LVEF, LVEDV, and LVESV will be provided for all cardiac MRI's obtained in the study to the physicians. Sites will also send Myocardial Solutions, Inc. de-identified information about the patients' medical history (i.e. comorbidities, past/current medications, etc.). In addition to Myocardial Solutions, Inc. reviewing the cardiac MRI images, due to the multi-departmental nature of this study, sites may also choose to obtain a clinical read on the research cardiac MR images obtained on the short axis, which are the same images that would be obtained in a clinical MRI, and provide only the LVEF, LVEDV, and LVESV for all subjects, regardless of randomization arm, and those values may be uploaded to the patients' medical record, if permitted. Doing so would then allow patients' oncology team access to this information in lieu of obtaining additional testing (i.e. clinical cardiac MRI's, echocardiograms, etc.) to obtain this same information.
	Page 18 **Figure 2** Clarified: Clarified randomization pathway vs. screen failure pathway after the second inclusion criteria is met.
Page 22 **Section 8** Original: The following steps must be taken before registering patients to this study: 1. Registration of patient in the Siteman Cancer Center OnCore database 2. Confirmation of patient eligibility by Washington University	**Page 22** **Section 8** Modified: The following steps must be taken in order to ~~before~~ register~~ing~~ patients to this study: 1. Confirmation of patient eligibility by site PI 2. Consent of patient to PROACT study 3. Confirmation of patient eligibility by Washington University 4. Assignment of Participant ID 5. Registration of ~~patient~~ participant in the Siteman Cancer Center OnCore database Added: Once the patient has been entered into the Siteman Cancer Center OnCore database, the coordinating center's coordinator will forward verification of enrollment and the subject ID.
Page 23 **Section 8.1** Original: Section 8.2 Confirm patient eligibility by collecting the information listed below and scanning and emailing it to the coordinating center's coordinator at least one business day prior to randomizing the patient: 1. Your name and contact information (telephone number, fax number, and email address) 2. Your site PI's name, the registering investigator's name, and your institution name 3. Patient's race, sex, and DOB 4. Three letters (or two letters and dash) for the patient's initials 5. Currently approved protocol version date 6. Copy of signed consent form (patient name may be blacked out) 7. Completed eligibility checklist, signed and dated by a member of the study team 8. Copy of appropriate source documentation confirming patient eligibility The coordinating center will email the participating site with verification of eligibility of the patient within 1 business day. Once verification of eligibility has been received, the patient can be randomized.	**Page 23** **Section 8.1** Modified: Moved to Section 8.1 Confirm patient eligibility by collecting the information listed below and scanning and emailing it to the coordinating center's coordinator at least one business day prior to the patient's baseline MRI scan: 1. Your name and contact information (telephone number, fax number, and email address) 2. Your site PI's name, the registering investigator's name, and your institution name 3. Patient's race, sex, and DOB 4. Three letters (or two letters and dash) for the patient's initials 5. Currently approved protocol version date 6. Copy of signed consent form 7. Completed eligibility checklist, signed and dated by a member of the study team 8. Copy of appropriate source documentation confirming patient eligibility The coordinating center will email the participating site with verification of eligibility of the patient within 1 business day. Once verification of eligibility has been received, the patient ~~can be randomized~~ will be registered into OnCore and the patient may undergo the baseline MRI scan.
Page 23 **Section 8.2** Original: Section 8.1 Registrations may be submitted Monday through Friday between 8am and 5pm CST. Urgent late afternoon or early morning enrollments should be planned in advance and coordinated with the Washington University research coordinator. Registration will be confirmed by the research coordinator or his/her delegate by email within 1 business day.	**Page 23** **Section 8.2** Modified: Moved to Section 8.2 Registrations may be submitted Monday through Friday between 8am and 5pm CST. Urgent late afternoon or early morning enrollments should be planned in advance and coordinated with the Washington University research coordinator. Registration will be confirmed by the research coordinator or his/her delegate

All patients at all sites must be registered after the patient has been consented, prior to the baseline MRI scan.	by email within 1 business day. Verification of eligibility and registration should be retained in the participant's study chart. All patients at all sites must be registered through the Siteman Cancer Center OnCore database at Washington University after the patient has been consented, prior to the baseline MRI scan.
	Page 23 **Section 8.3** Added: Each patient will be identified with a unique Participant ID for this study. The Participant ID will be based on the patient's Participant ID in the SURVIVE Registry, as well as the patient's enrollment number in the PROACT study. All data will be recorded with this Participant ID on the appropriate CRFs.
Page 26 **Section 9.4.3** Original: The research team at a participating site is responsible for following its site's guidelines for reporting applicable events to its site's IRB according to its own institutional guidelines.	**Page 26** **Section 9.4.3** Modified: The research team at a participating site is responsible for following its site's guidelines for reporting applicable events to its site's IRB according to its own institutional guidelines. Since sites will be relying on Washington University's IRB, any reportable event will also be submitted to Washington University's IRB for review.
Page 27 **Section 10.1.2** Original: Data monitoring will be conducted by the coordinating center and will consist of data checks, both electronic and manual. Every 6 months, data entered into the REDCap database will be reviewed for accuracy by designated study staff at the coordinating center. Uploaded source documentation by participating sites will also be reviewed for inconsistent data, if applicable. If there are inconsistencies or missing values, queries will be issued to the participating sites and they will refer to the subject's records to correct the aberration. Participating sites are expected to enter data into REDCap within 14 business days of a study visit. Sites that appear to have significant delays between the time of enrollment/study visits and data entry will be contacted by the coordinating center. Participating sites are also expected to respond to any REDCap queries within 1 month of issuance. Sites that appear to have a significant amount of REDCap queries will be contacted by the coordinating center. At each interval, the coordinating center will note the number of participants accrued to date as well as the number of participants accrued for that 6 months interval.	**Page 27** **Section 10.1.2** Added: Data and regulatory documents from all participating sites will be reviewed by the Washington University Quality Assurance and Safety Monitoring Committee (QASMC) every 6 months. For participating sites added on after study initiation, the first review for that site will take place during the next scheduled QASMC review, which may occur prior to 6 months after site initiation. Because all monitoring will take place remotely, uploads of source documentation, including consent forms with signatures, either to REDCap and/or WUSTL Box will be mandatory for participating sites. In addition, QASMC may request access to participating sites' electronic medical record, if the site's institution allows such access. Modified: Data and regulatory document monitoring will also be conducted by the coordinating center's research coordinators and will consist of data checks, both electronic and manual. Every 6 months prior to QASMC review, data entered into the REDCap database will be reviewed for accuracy by designated study staff at the coordinating center. As with QASMC audits, for participating sites added on after study initiation, the first review for that site will take place during the next scheduled data review. Uploaded source documentation, including consent forms with signatures, by participating sites will also be reviewed for inconsistent data~~, if applicable~~. If there are inconsistencies or missing values, queries will be issued to the participating sites and they will refer to the subject's records to correct the aberration. Participating sites are expected to enter data into REDCap within 14 business days of a study visit. Sites that appear to have significant delays between the time of enrollment/study visits and data entry will be contacted by the coordinating center. Participating sites are also expected to respond to any REDCap queries within 1 month of issuance. Sites that appear to have a significant amount of REDCap queries will be contacted by the coordinating center. At each interval, the coordinating center will note the number of participants accrued to date as well as the number of participants accrued for that 6 months interval.
Page 27 **Section 10.1.3** Original: In compliance with the Washington University Institutional Data and Safety Monitoring Plan, the Data and Safety Monitoring Committee (DSMC) will meet to review data semi-annually beginning six months after accrual has begun. The report will include: • HRPO protocol number, protocol title, Principal Investigator name, and research coordinator name • Date of initial HRPO approval, date of most recent HRPO approval/revision of consent, date of HRPO expiration, and study status • History of study including summary of substantive amendments; summary of accrual suspensions including start/stop dates and reason • Study-wide target accrual and study-wide actual accrual • Protocol activation date • Average rate of accrual observed in Year 1, Year 2, and subsequent years • Expected accrual end date • Objectives of protocol with supporting data and list of the number of participants who have met each objective • Measures of efficacy	**Page 27** **Section 10.1.3** Modified: In compliance with the Washington University Institutional Data and Safety Monitoring Plan, the Principal Investigator will provide a Data and Safety Monitoring ~~Committee~~ (DSM~~C~~) report to the Washington University Quality Assurance and Safety Monitoring Committee (QASAMC) ~~will meet to review data~~ semi-annually beginning six months after accrual has opened (if at least 5 patients have been enrolled) or 1 year after accrual has opened (if fewer than 5 patients have been enrolled at the 6 month mark) ~~begun~~. The Principal Investigator will review all patient data at least every 6 months, and provide a semi-annual report to QASMC. The report will include: • HRPO protocol number, protocol title, Principal Investigator name, and research coordinator name • Date of initial HRPO approval, date of most recent HRPO approval/revision of consent, date of HRPO expiration, date of most recent QA audit, ~~and~~ study status, and phase of study • History of study including summary of substantive amendments; summary of accrual suspensions including start/stop dates and reason; and summary of protocol exceptions, error, or breach of confidentiality including start/stop dates and reason • Study-wide target accrual and study-wide actual accrual • Protocol activation date

• Abstract submissions/publications • Summary of any recent literature that may affect the safety or ethics of the study	• Average rate of accrual observed in Year 1, Year 2, and subsequent years • Expected accrual end date • Objectives of protocol with supporting data and list of the number of participants who have met each objective • ~~Measures of efficacy~~ • Abstract submissions/publications • Summary of any recent literature that may affect the safety or ethics of the study

Amendment 3: Version 4.0 01/24/2020

Summary of Changes	
Protocol v3.0	**Protocol v4.0**
Page 1 **Data and Safety Monitoring Committee** Original: Gregory Ewald, MD, FACC Washington University Cardiology Edward Geltman, MD Washington University Cardiology Justin Vader, MD Washington University Cardiology	**Page 1** **Data and Safety Monitoring Committee** Modified: ~~Gregory Ewald, MD, FACC Washington University Cardiology~~ Edward Geltman, MD Washington University Cardiology Manik Amin, MD Washington University Cardiology Elena Deych Washington University Cardiology Statistician ~~Justin Vader, MD Washington University Cardiology~~
Page 9 **1.3 Study Design** Original: Breast cancer, lymphoma, sarcoma, leukemia, myeloma, and lung cancer patients scheduled to receive anti-cancer therapy, who are previously enrolled in the SURVIVE Registry, will be screened for study participation. **1.5 Endpoints** Original: The primary efficacy endpoint is the sensitivity of detection of patients with myocardial dysfunction using MyoStrain® compared to standard assessments of cardiac function: left ventricular ejection fraction (LVEF), as well as end-systolic (LVESV) and end-diastolic (LVEDV) volumes.	**Page 10** **1.3 Study Design** Modified: ~~Breast cancer, lymphoma, sarcoma, leukemia, myeloma, or lung cancer patients~~ Patients with any type of cancer scheduled to receive anti-cancer therapy, who are previously enrolled in the SURVIVE Registry, will be screened for study participation. **1.5 Endpoints** Modified: The primary efficacy endpoint is the sensitivity and accuracy of detection of patients with myocardial dysfunction using MyoStrain® compared to standard assessments of cardiac function: left ventricular ejection fraction (LVEF), as well as end-systolic (LVESV), and end-diastolic (LVEDV), and stroke (LVSV) volumes indexed to body surface area. Changes in function based on clinical presentation, standard assessments, and all available metrics will be used to define the cardiotoxicity status of the patient. A clinical committee organized and chaired by the principal investigator will be used to classify each exam in both unblinded and blinded arms according to professional knowledge and derived from the ASE Expert Consensus Position Paper, the ESC Position Paper, and the ESMO Clinical Practice Guidelines. [1] [2] [3] • Clinical cardiac dysfunction is defined as an absolute change in LVEF > 10% from baseline to below 53% combined with heart failure symptoms or abnormal cardiac biomarkers (troponin, BNP, or NT pro BNP). • Subclinical CTX was defined as an asymptomatic patient with a greater than 15% decrease in LVEF that remains >= 53%, worsening GLS more than 15% from baseline, or abnormal cardiac biomarkers (troponin, BNP, or NT pro BNP). If no baseline information is available to compare metrics for categorizing cardiotoxicity status, considering most patients in the PROACT sub-study of the Survive Registry will have metastatic cancer with prior treatments including chemotherapy, physician discretion and patient presentation will provide the final decision on cardiotoxicity category. All available metrics will be used to classify patients at each assessment time point.
Page 9 **1.6 Inclusion Criteria** Original: 3) Histological diagnosis of early or metastatic breast cancer, lymphoma, sarcoma, leukemia, myeloma, or lung cancer (patients with treated and clinically stable brain metastasis are acceptable)	**Page 11** **1.6 Inclusion Criteria** Modified: 3) Histological diagnosis of ~~early or metastatic breast cancer, lymphoma, sarcoma, leukemia, myeloma, or lung~~ any cancer type (patients with treated and clinically stable brain metastasis are acceptable) **1.7 Exclusion Criteria** Added/Clarified: Note: If a patient develops a temporary contraindication (e.g. temporary tissue expanders in breast cancer patients) after the baseline MRI, follow up MRIs will be discontinued for safety for the duration in which the patient has the contraindication. However, once the patient is no longer contraindicated to receiving MRIs, the study schedule may resume with their next scheduled MRI time point from the date of enrollment. Therefore, some time points may be skipped during the patient's enrollment in the study. Also, if a patient needs a repeat MRI at any time point for any reason (i.e. panic attack during the MRI causing them to not be able to continue,

	unreadable images, etc.), we may repeat the MRI as long as the patient is willing.
Page 18 **5.1 Summary Protocol** Original: Breast cancer, lymphoma, sarcoma, leukemia, myeloma, or lung cancer patients scheduled to receive anti-cancer therapy with or without concomitant radiotherapy and enrolled in the SURVIVE Registry will be evaluated based on baseline MyoStrain segmental dysfunction risk profile.	**Page 19** **5.1 Summary Protocol** Original: ~~Breast cancer, lymphoma, sarcoma, leukemia, myeloma, or lung cancer patients~~ Patients with any type of cancer scheduled to receive anti-cancer therapy with or without concomitant radiotherapy and enrolled in the SURVIVE Registry will be evaluated based on baseline MyoStrain segmental dysfunction risk profile.
Page 21 **5.4 Inclusion Criteria** 3) Histological diagnosis of early or metastatic breast cancer, lymphoma, sarcoma, leukemia, myeloma, or lung cancer (patients with treated and clinically stable brain metastasis are acceptable)	**Page 23** **5.4 Inclusion Criteria** 3) Histological diagnosis of ~~early or metastatic breast cancer, lymphoma, sarcoma, leukemia, myeloma, or lung~~ any cancer type (patients with treated and clinically stable brain metastasis are acceptable) **5.5 Exclusion Criteria** Added/Clarified: Note: If a patient develops a temporary contraindication (e.g. temporary tissue expanders in breast cancer patients) after the baseline MRI, follow up MRIs will be discontinued for safety for the duration in which the patient has the contraindication. However, once the patient is no longer contraindicated to receiving MRIs, the study schedule may resume with their next scheduled MRI time point from the date of enrollment. Therefore, some time points may be skipped during the patient's enrollment in the study. Also, if a patient needs a repeat MRI at any time point for any reason (i.e. panic attack during the MRI causing them to not be able to continue, unreadable images, etc.), we may repeat the MRI as long as the patient is willing.
Page 27 **Statistical Considerations** Original: …Furthermore, we will use decision trees for identifying the importance of MyoStrain cardiac features compared to cardiac toxicity risk prediction based on standard assessment of variables LVEF, LVESV, and LVEDV… Original: The sensitivity, specificity, and diagnostic accuracy of each reader to detect changes in myocardial function will be determined for quantitative SENC-CMR. Cutoff-values used to calculate sensitivity and specificity of the quantitative SENC parameters will be determined using data previously published. McNemar's test with continuity correction will be used to compare the diagnostic performance of each of the SENC-CMR cutoff parameters. Additionally, Receiver Operating Characteristic curves will be generated to calculate and compare the area under the curves to determine the diagnostic performance of changes in various strain parameters. Inter- and intra-observer variability will also be determined for each of the above parameters using intraclass correlation.	**Page 30** **Statistical Considerations** Modified: …Furthermore, we will use decision trees for identifying the importance of MyoStrain cardiac features compared to cardiac toxicity risk prediction based on standard assessment of variables LVEF, LVESV, ~~and~~ LVEDV, and LV Stroke Volume Index (LVSVi). Endpoints will be evaluated based on discrete variables of MyoStrain values versus standard assessments. Considering many patients will have a complex management of cardioactive medications as well as cancer treatment regimen, the classification of cardiotoxicity status will be based on a clinical committee to designate whether the patient experienced no cardiotoxicity, functional decline without cardiotoxicity, subclinical cardiotoxicity, or clinical cardiac dysfunction at each exam time point… Modified: The sensitivity, specificity, and diagnostic accuracy of each reader to detect changes in myocardial function will be determined for quantitative SENC-CMR. Cutoff-values used to calculate sensitivity and specificity of the quantitative SENC parameters ~~will be~~ were determined using data previously published. The cutoff for the % of MyoStrain segments <= -17% (based on 37 left ventricular segments) in detecting subclinical cardiotoxicity in the PREFECT50 planned interim analysis was 68% and the cutoff for detecting clinical cardiac dysfunction was 49%; a cutoff of 80% differentiates normal cardiac function from patients experiencing functional decline. McNemar's test with continuity correction will be used to compare the diagnostic performance of each of the SENC-CMR cutoff parameters. Additionally, Receiver Operating Characteristic curves as well as Precision Recall curves will be generated to calculate and compare the area under the curves to determine the diagnostic performance of changes in ~~various~~ strain parameters and standard assessments. Inter- and intra-observer variability will also be determined for each of the above parameters using intraclass correlation.

Amendment 4: Version 5.0 04/13/2020

Summary of Changes	
Protocol v4.0	**Protocol v5.0**
Page 20 **5.1 Summary Protocol** Original: Patient's will continue to undergo MyoStrain® MRI testing, regardless of study arm, at 1 month (± 1 week), 3 months (± 1 week), 6 months (± 1 week), 12 months (± 30 days), 24 months (± 30 days), and 36 months (± 30 days) after the baseline visit.	**Page 20** **5.1 Summary Protocol** Modified: Patient's will continue to undergo MyoStrain® MRI testing, regardless of study arm, at 1 month (± 2 weeks ~~1 week~~), 3 months (± 2 weeks ~~1 week~~), 6 months (± 2 weeks ~~1 week~~), 12 months (± 30 days), 24 months (± 30 days), and 36 months (± 30 days) after the baseline visit.
Page 22 **5.1 Summary Protocol**	**Page 22** **5.1 Summary Protocol** Modified: Changed time point windows for 1 month, 3 month, and 6 month time points in the PROACT Schedule of Events chart from ± 1 week to ± 2 weeks.

Amendment 5: Version 6.0 09/27/2021

Summary of Changes	
Protocol v5.0	**Protocol v6.0**
Page 1 **Principal Investigator:** Original: **Daniel J. Lenihan, MD, FACC** Professor of Medicine Cardiovascular Division Director, Cardio-Oncology Center of Excellence Advanced Heart Failure Clinical Research **Phone:** +1 (314) 362-1291 **Email:** djlenihan@wustl.edu **Data and Safety Monitoring Committee:** Original: Manik Amin, MD Original: *This protocol was co-written by Susan F. Dent, MD, FRCPC, Medical Oncologist at Ottawa Hospital Cancer Center.*	**Page 1** **Principal Investigator:** Modified: ~~**Daniel J. Lenihan, MD, FACC**~~ **Joshua Mitchell, MD, MSCI, FACC, FICOS** Assistant Professor of Medicine Cardiovascular Division Interim Director, Cardio-Oncology Center of Excellence ~~Advanced Heart Failure~~ ~~Clinical Research~~ **Phone:** +1 (314) 362-1291 **Email:** ~~djlenihan@wustl.edu~~ jdmitchell@wustl.edu **Data and Safety Monitoring Committee:** Modified: ~~Manik Amin, MD~~ Nusayba Bagegni, MD Modified: *This protocol was co-written by Daniel J. Lenihan, MD, FACC and Susan F. Dent, MD, FRCPC, Medical Oncologist at Ottawa Hospital Cancer Center.*
Page 7 **Investigator's Signature Page:** Original: Name: Daniel J. Lenihan, MD, FACC Name: Vlad Zaha, MD, PhD, FACC, FASE, FHFSA Title: Clinical Site Investigator (University of Texas Southwestern) Name: Lauren Baldassarre, MD, FACC, FSCMR, FSCCT Title: Clinical Site Investigator (Yale) Name: Vijay Rao, MD, PhD, FACC, FASE, FHFSA Title: Clinical Site Investigator (Franciscan St. Francis Health)	**Page 8** **Investigator's Signature Page:** Modified: Name: ~~Daniel J. Lenihan, MD, FACC~~ Joshua Mitchell, MD, MSCI, FACC, FICOS ~~Name: Vlad Zaha, MD, PhD, FACC, FASE, FHFSA~~ ~~Title: Clinical Site Investigator (University of Texas Southwestern)~~ ~~Name: Lauren Baldassarre, MD, FACC, FSCMR, FSCCT~~ ~~Title: Clinical Site Investigator (Yale)~~ ~~Name: Vijay Rao, MD, PhD, FACC, FASE, FHFSA~~ ~~Title: Clinical Site Investigator (Franciscan St. Francis Health)~~
Page 11 **1.8 Expected Duration** Original: Based on an enrollment of 102 eligible patients (a subset of the approximately 700 SURVIVE Registry patients enrolled annually across all SURVIVE participating sites)…	**Page 12** **1.8 Expected Duration** Modified: Based on an enrollment of ~~102 eligible~~ 40 evaluable patients (a subset of the approximately 700 SURVIVE Registry patients enrolled annually across all SURVIVE participating sites)…
Page 24 **5.6 Duration of the study for the subject** Original: Based on an enrollment of 102 eligible patients (a subset of the approximately 700 SURVIVE Registry patients enrolled annually across all SURVIVE participating sites)… **5.7 Sample size** Original: 102 patients will be randomized 1:1 to the MyoStrain® imaging guided arm versus the standard of care arm.	**Page 25** **5.6 Duration of the study for the subject** Modified: Based on an enrollment of ~~102 eligible~~ 40 evaluable patients (a subset of the approximately 700 SURVIVE Registry patients enrolled annually across all SURVIVE participating sites)… **5.7 Sample size** Modified: ~~102~~ 40 evaluable patients will be randomized 1:1 to the MyoStrain® imaging guided arm versus the standard of care arm.

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Principal Investigator's Signature Page

The study will be conducted in accordance with the International Conference on Harmonisation guidelines for Good Clinical Practice (ICH E6), the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), and the NIDCR Clinical Terms of Award. All personnel involved in the conduct of this study have completed human subject's protection training.

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Principal Investigator and Clinical Site Investigators:

Signed: _____ Date: _____

Name: Joshua Mitchell, MD, MSCI, FACC, FICOS
Title: Principal Investigator

TABLE OF CONTENTS

1. SUMMARY

1.1. Study Purpose

This study is intended to evaluate the ability of a new analysis package with cardiac MRI to assist in the early detection and management of cardiotoxicity from therapeutics used to treat cancer.

1.2. Study Device and Intended Use

Common Name: Cardiac MRI Imaging Software

Trade Name: MyoStrain®

Regulatory Status: The MyoStrain® SENC CMR Imaging System is limited to observational evaluation within the United States. MyoStrain® has European approval with an EC Certificate according to Directive 93/42/EEC on Medical Devices, Annex II excluding Section 4 (CE 657862) in respect of: Design, development and manufacture of software for the quantification of cardiac MRI images.

Intended Use: MyoStrain® SENC software receives image data from MRI storage archives and performs viewing, image manipulation, communication, printing, and quantification of images. Available measurements include longitudinal and circumferential strain to quantitatively describe the wall motion of the heart. Tools are provided for display of regional motion properties of the heart.

A report interface is provided. Measurement tools provide information that can be output in standardized or specialized report formats. This interface makes it possible to quickly and reliably fill out a complete clinical report of a cardiac imaging exam with strain. The results of the measurement tools are interpreted by the physician and can be communicated to referring physicians to support the determination of a diagnosis.

1.3. Study Design

This is a prospective, multi-center, open label, randomized study. The study will enroll patients who exhibit subclinical myocardial dysfunction at baseline as determined by MyoStrain® evaluation.

Patients with any type of cancer scheduled to receive anti-cancer therapy, who are previously enrolled in the SURVIVE Registry, will be screened for study participation. Consented subjects meeting all inclusion/exclusion criteria will be enrolled into the PROACT study. Subjects will be randomized 1:1 between the MyoStrain® guided treatment arm and MyoStrain® observational arm. Patients in both randomized study arms will be followed with MyoStrain® testing at baseline, 1, 3, 6, 12, 24 & 36 month follow-ups, as outlined in the protocol.

1.4. Objectives

The primary objectives of this study are:

1. to robustly quantify myocardial function in cancer patients scheduled to receive anti-cancer therapy
2. to determine the ability of MyoStrain® testing to detect subclinical cardiac dysfunction compared to standard cardiac imaging
3. to determine the impact of MyoStrain® imaging on medical management of cardiotoxicity through early detection of at risk patients

1.5. Endpoints

The primary efficacy endpoint is the sensitivity and accuracy of detection of patients with myocardial dysfunction using MyoStrain® compared to standard assessments of cardiac function: left ventricular ejection fraction (LVEF), as well as end-systolic (LVESV), end-diastolic (LVEDV), and stroke (LVSV) volumes indexed to body surface area.

Changes in function based on clinical presentation, standard assessments, and all available metrics will be used to define the cardiotoxicity status of the patient. A clinical committee organized and chaired by the principal investigator will be used to classify each exam in both unblinded and blinded arms according to professional knowledge and derived from the ASE Expert Consensus Position Paper, the ESC Position Paper, and the ESMO Clinical Practice Guidelines. [1] [2] [3]

- Clinical cardiac dysfunction is defined as an absolute change in LVEF > 10% from baseline to below 53% combined with heart failure symptoms or abnormal cardiac biomarkers (troponin, BNP, or NT pro BNP).
- Subclinical CTX was defined as an asymptomatic patient with a greater than 15% decrease in LVEF that remains >= 53%, worsening GLS more than 15% from baseline, or abnormal cardiac biomarkers (troponin, BNP, or NT pro BNP).
- If no baseline information is available to compare metrics for categorizing cardiotoxicity status, considering most patients in the PROACT sub-study of the Survive Registry will have metastatic cancer with prior treatments including chemotherapy, physician discretion and patient presentation will provide the final decision on cardiotoxicity category. All available metrics will be used to classify patients at each assessment time point.

1.6. Inclusion Criteria

1) Participant in the SURVIVE registry
2) Signed consent form for PROACT
3) Histological diagnosis of any cancer type (patients with treated and clinically stable brain metastasis are acceptable)
4) Scheduled to receive anti-cancer therapy (radiation therapy is permitted)

1.7. Exclusion Criteria

1) Contraindication to magnetic resonance imaging (MRI)
2) Unable to comply with study investigations (in the judgment of the investigator)
3) Life expectancy less than 1 year

Note: If a patient develops a temporary contraindication (e.g. temporary tissue expanders in breast cancer patients) after the baseline MRI, follow up MRIs will be discontinued for safety for the duration in which the patient has a contraindication. However, once the patient is no longer contraindicated to receiving MRIs, the study schedule may resume with their next scheduled MRI time point from date of enrollment. Therefore, some time points may be skipped during the patient's enrollment in the study.

Also, if a patient needs a repeat MRI at any time point for any reason (i.e. panic attack during the MRI causing them to not be able to continue, unreadable images, etc.), we may repeat the MRI as long as the patient is willing.

1.8. Expected Duration

Based on an enrollment of 40 evaluable patients (a subset of the approximately 700 SURVIVE Registry patients enrolled annually across all SURVIVE participating sites) who demonstrate moderate to high risk of cardiotoxic effects during cardio-oncology treatment due to observed segmental dysfunction on baseline MyoStrain® evaluation, it is anticipated that all subjects will be enrolled within 12 months after study initiation. The study will end when the last enrolled subject completes the 36-month follow-up, data is analyzed and reports are written. Therefore, study duration is anticipated to be approximately 54 months.

2. DEVICE DESCRIPTION

For all patients undergoing a cardiac MRI, a standard non-contrast protocol will be used to acquire a full cardiac volume for chamber sizes and LVEF in the short axis as the initial scan.

2.1. MyoStrain® SENC CMR Imaging System

The MyoStrain® SENC CMR Imaging System is limited to observational evaluation within the United States. MyoStrain® has been approved with an EC Certificate according to Directive 93/42/EEC on Medical Devices, Annex II excluding Section 4 (CE 657862) in respect of: Design, development and manufacture of software for the quantification of cardiac MRI images.

Strain Encoding (SENC) MRI technology is a fast MRI scanning diagnostic test that measures the contraction of the heart muscle in one heartbeat per image plane. This means that patients can be scanned very fast while breathing, and a complete view of the ventricles' health can be obtained in less than 6 seconds. Quantitative assessment of the strength of the heart muscle can have many clinical applications, but its highest value is in the two largest heart disease populations: those patients with heart failure and coronary artery disease.

SENC is an MRI Pulse Sequence for Strain Encoding

- A pulse sequence is an algorithm that instructs the MRI scanner to acquire certain types of images. Any MRI scanner has a large number of pulse sequences for general and specialized imaging of different parts of the body. They produce images that show different anatomies, physiologies, or pathologies of the different tissues of the body. For imaging the heart, there is a group of specialized pulse sequences that can show different aspects of the heart, including, but not limited to, the structure of the heart, the motion of the heart, the tissue characterization of the muscle, the flow of the blood, the structure of the vessels, and more.
- The Strain Encoding (SENC) pulse sequence is a specialized pulse sequence that produces images of the heart muscle that reveal the underlying contraction of the muscle of a healthy heart and associated weaknesses in case of disease. The measurements of the deformations of regions within the heart muscle ("myocardium") associated by contraction and relaxation during a single heartbeat is measured by the mechanical quantity called "strain."
- Myocardial Solutions, Inc. software measures tissue deformation or "strain" from the pulse sequence images. Quantitatively, "strain" is a mechanical property of deforming objects and measured as the percentile change in spacing between two points on a deforming object. For example, when muscle contracts, the muscle length is shortened. For example, a 30% shortening of the muscle is measured as strain of negative 30%.
- Measuring the shortening of the Heart Muscle results in two parameters that SENC quantifies: circumferential and longitudinal strain. Strain measurement depends on "direction" of measuring. For measuring the contraction of the heart muscle, there are two main directions that are typically used: 1) longitudinal strain, which describes the contraction of the myocardium that contributes to the base-to-apex contraction of the heart chambers; 2) circumferential strain, which describes the contraction of heart muscle fibers around the circumference of the chambers of the heart.
- Using SENC, segmental circumferential and longitudinal strain values in 37 regions are measured in 6 seconds.

The Intended Use of the MyoStrain® SENC MRI acquisition is:

- MyoStrain® SENC software receives image data from MRI storage archives and performs viewing, image manipulation, communication, printing, and quantification of images. Available measurements include longitudinal and circumferential strain to quantitatively describe the wall motion of the heart. Tools are provided for display of regional motion properties of the heart.
- A report interface is provided. Measurement tools provide information that can be output in standardized or specialized report formats. This interface makes it possible to quickly and reliably fill out a complete clinical report of a cardiac imaging exam with strain. The results of the measurement tools are interpreted by the physician and can be communicated to referring physicians to support the determination of a diagnosis.

2.2. Background Clinical & Preclinical Testing

Myocardial Solutions, Inc. (MSI) MyoStrain® Software was implemented with SENC MRI acquisition using source codes that were developed at Johns Hopkins University. Both Diagnosoft, before, and MSI, today, continue to use the original SENC strain source code. SENC pulse sequence patches, derived from the SENC source code, designed for Philips MRI Scanners, have been validated with extensive clinical and preclinical testing.

The MSI software leverages prior SENC image acquisition and processing functions that have been extensively studied on volunteers, phantoms studies, and clinical applications. The Fast SENC software processes images obtained with the well-studied SENC pulse sequence patch, which has supported several publications demonstrating the utility of strain imaging for various clinical applications.

Implementation of the SENC MRI acquisition in the Myocardial Solutions SENC Software has been validated as evidenced by literature across three separate comparisons: Comparisons with 1) Diagnosoft HARP, a 510k FDA certified software for measuring strain from tagged MR images; 2) EchoPAC STE, a certified software from GE Vingmed for measuring strain using speckle tracking methods; and 3) various physiological and pathological indicators.

Validation of MyoStrain® SENC relative to Diagnosoft HARP

1. Diagnosoft HARP is a 510k certified software for the analysis of MR Tagging images of the heart and measuring the strain that reveals the deformation of the myocardium as the heart muscle contracts and relaxes. Diagnosoft HARP is considered to be the gold standard for measuring regional strain and there are over 100 peer-reviewed published studies on the use of strain from HARP.
2. Published Comparisons: SENC versus Diagnosoft HARP compared the strain measurements from SENC to strain calculated by MR Tagging and Diagnosoft HARP software. [4] [5] [6] The comparisons

showed strong correlation in measurements of strain, both regional and global, and also the different strain measurements, such as longitudinal and circumferential strain; the correlation between SENC and tagged MRI was significant with R=0.90.

3. The published literature demonstrates that SENC strain measurements are comparable to those obtained used MR Tagging and HARP software, which is considered to be the gold standard method for measuring strain. SENC strain software has advantages over HARP software by providing the comparable strain results with faster acquisition and analysis. The SENC strain test takes as little as 10 minutes including analysis, which can be performed by a technologist, while HARP would require much longer testing and more specialized expertise to analyze. SENC strain is much more patient- and user-friendly requiring only a single heartbeat for image acquisition, eliminating the need for patient breath holding.

Comparison of SENC to EchoPAC, GE Vingmed STE

4. EchoPAC is a 510k and CE Mark certified package form GE Vingmed for the processing of echocardiographic images and films. It can measure the deformation and strain of tissue using speckle tracking echocardiography (STE), which is an image post-processing algorithm.
5. Published Comparisons: SENC versus EchoPAC STE compares the strain measurements from SENC to the strain calculated using Tissue Strain Echocardiography (STE). [7] STE was calculated using EchoPAC software from GE.
6. Cardiac MRI measurements of strain using SENC and MR tagging are considered to be equivalent to STE or better due to the excellent image of cardiac tissue by MRI and creation of actual physical markers inside the tissue to measure strain. STE is an image processing method that tries to extract motion and strain from conventional echocardiographic movies with their known image quality limitations.
7. The published comparisons showed a correlation between strain measurements obtained by SENC and those calculated by STE. It is important to point out that MRI, as a gold standard method, was used as the reference for measuring strain. STE post-processing calculations were expected to be inherently inferior as it inherits some of the suboptimal image qualities of echocardiography (relative to MRI).

Validation of MyoStrain® SENC Based on Clinical Physiological and Pathological Indicators

8. SENC strain was directly compared to different physiological and pathological indicators to understand the mechanics of the heart muscle and alterations due to underlying disease and pathology. This includes the understanding of the contraction of the left and right ventricles, changes in strain in the case of myocardial infarction as determined using delayed enhancement methods, and detection of ischemia in patients by utilizing stress testing.
9. Published Comparisons: SENC Strain for Physiological and Pathological Indicators. Different studies were done using SENC to understand the mechanics of the heart wall muscle and the changes that accompany certain diseases. In the case of coronary artery diseases, the studies showed changes in strain because of acute coronary artery syndrome that results in myocardial infarction.
10. Stress testing for ischemia, performed on patients with suspected or known ischemic heart disease, demonstrated that measured strain was more sensitive in detecting stenosis in the coronary arteries compared to 1) conventional cine movies with qualitative assessment of abnormal wall motion under stress, and 2) the outcomes of revascularization of positively diagnosed patients. [8] [9] [10] [11] [12]
11. Myocardial infarction studies show the value of strain measurements in assessing, with high accuracy, changes in regional function associated with damage from myocardial infarction. [13] [14] [15] [16] Quantification of changes in contraction is more accurate (more sensitive and specific) in associating with the depth of damage vis-à-vis subjective wall motion assessment. Figure 1 shows the composite strain scale based on comparison to late gadolinium enhancement analysis to differentiate segmental myocardial function into healthy with normal contraction (defined as normokinesia and hyperkinesia), at risk with abnormal contraction (hypokinesia), and impaired viability (akinesia and dyskinesia).

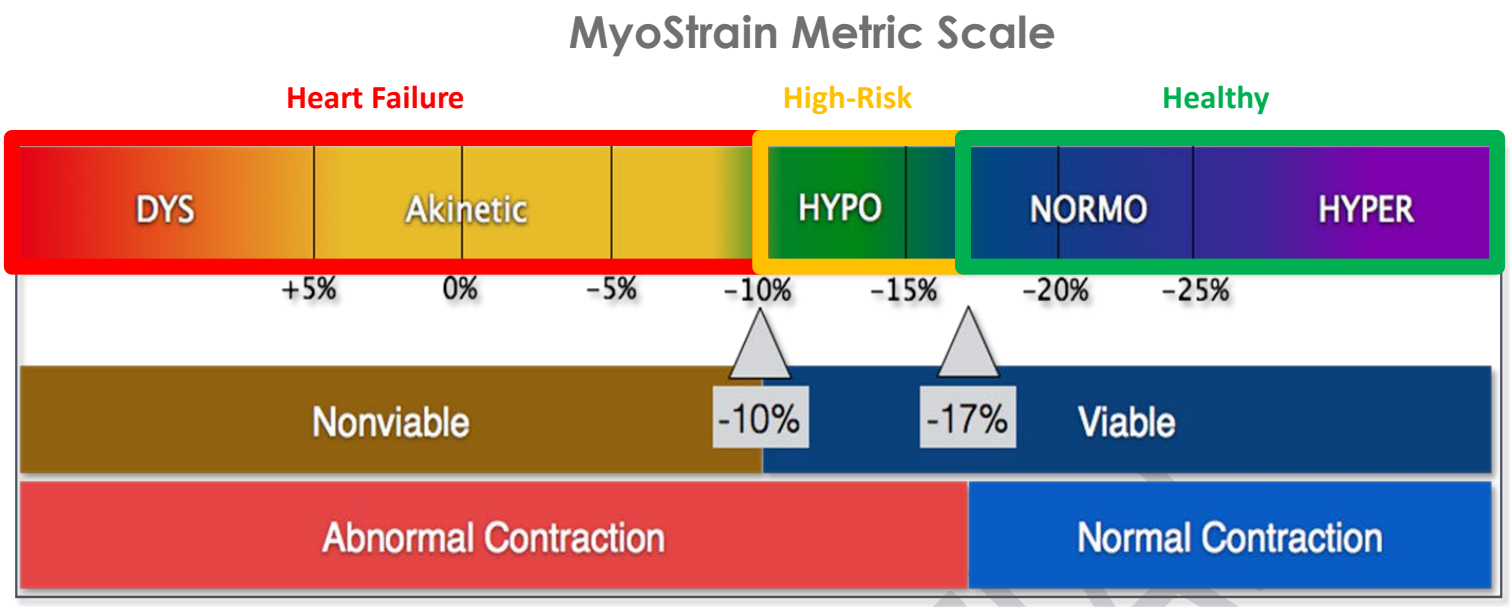


Figure 1 – MyoStrain® Segmental Scale of Myocardial Health

12. Cardiac mechanics studies illustrated other applications of SENC strain measurements in understanding the mechanics of the heart, especially the left and right ventricles. [17] [18] [19] [20] [21] These healthy subjects studies demonstrated, with high accuracy and precision, the ability to detect subtle variations in regional contraction. Also, quantification revealed variations in contractility as a result of diseases affecting the right ventricle, which is very hard to assess using echocardiography because of the position of the right ventricle close to the ribs and the sternum and its geometry.

2.3. PROACT Pilot Clinical Testing

A single center, pilot study was performed to evaluate the ability of the MyoStrain® MRI software system to identify cardiotoxicity during cardio-oncology treatment of breast cancer and lymphoma patients. An interim analysis of 15 subjects from the PROACT Pilot study (VAL-1005P) is included below to provide additional clinical evidence that the MyoStrain® software is able to detect progression of myocardial dysfunction resulting from cardiotoxicity. The pilot study was performed by Principal Investigator Hr. Priv.-Doz. Dr. Henning Steen (Facharzt für Innere Medizin, Kardiotogie PD DR) at Marien Krankenhaus GmbH (Hamburg, Germany).

- **Patient Demographics**

Demographic	Average ± St Dev
Age (years)	52.2 ± 11.5
Body Surface Area (m^2)	1.8 ± 0.2
Body Mass Index (kg/m^2)	25.7 ± 4.7
History of Cancer (months)	1.4 ± 0.8
Charlson Comorbidity Index	1.4 ± 1.0

- **Baseline CMR Information**

Baseline CMR Information	Average ± St Dev
LVEF (%)	58.8 ± 5.3
LVEDV Index (ml/m^2)	77.6 ± 13.4
LVESV Index (ml/m^2)	32.1 ± 8.0
Stroke Volume Index (ml/m^2)	45.5 ± 7.8
T1 Value Pre-Contrast (msec)	1052.4 ± 44.6
T1 St Dev Pre-Contrast (msec)	52.4 ± 11.8
Global Longitudinal Strain (%)	-20.8 ± 1.9
Global Circumferential Strain (%)	-19.0 ± 1.8

# Segments > -10%	1.7 ± 1.5
# Segments > -17%	8.5 ± 4.7

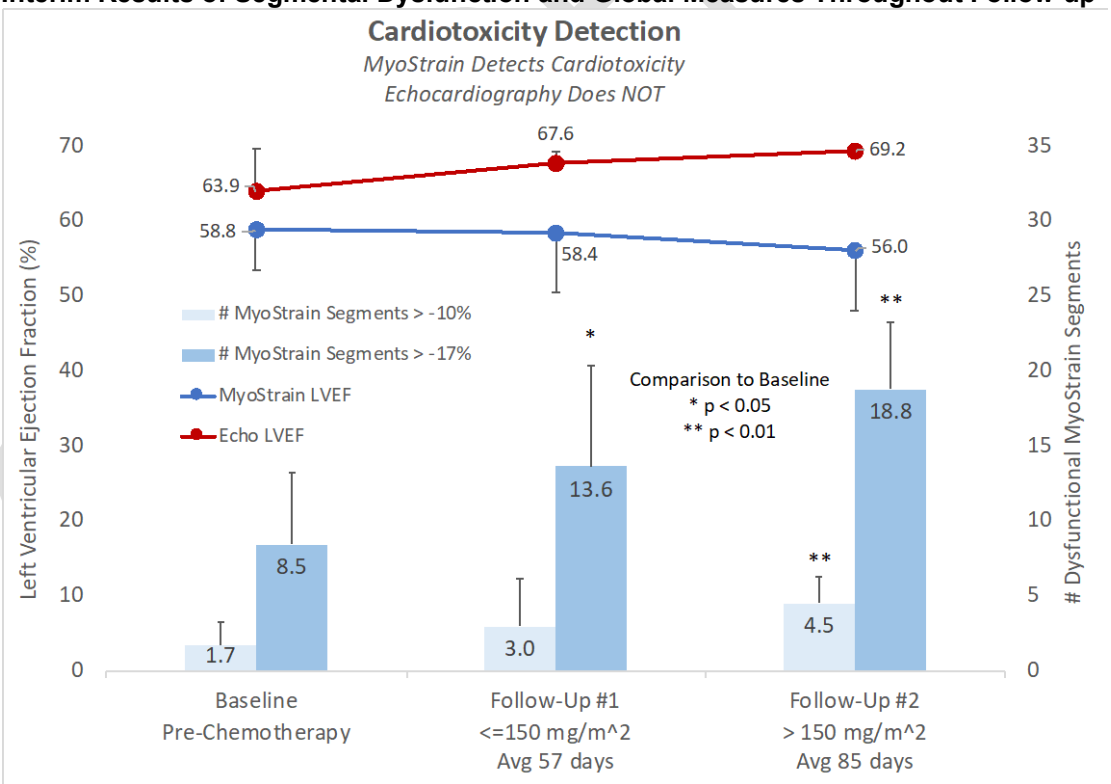
- **Baseline Risk Assessment of Developing Cardiotoxicity by Segmental MyoStrain®.** Patients were stratified as to their risk by the number of dysfunctional (> -10%) and abnormal segments (> -17%). These thresholds have been validated as previously described in Figure 1 above.

Cardiotoxicity Risk Level	Segmental MyoStrain® Criteria	Incidence
Low	≤ 1 Segment > -10% & < 9 Segments > -17%	46% (7/15)
Moderate	2-3 Segments > -10% or 9+ Segments > -17%	27% (4/15)
High	3+ Segments > -10% & 10+ Segments > -17%	27% (4/15)

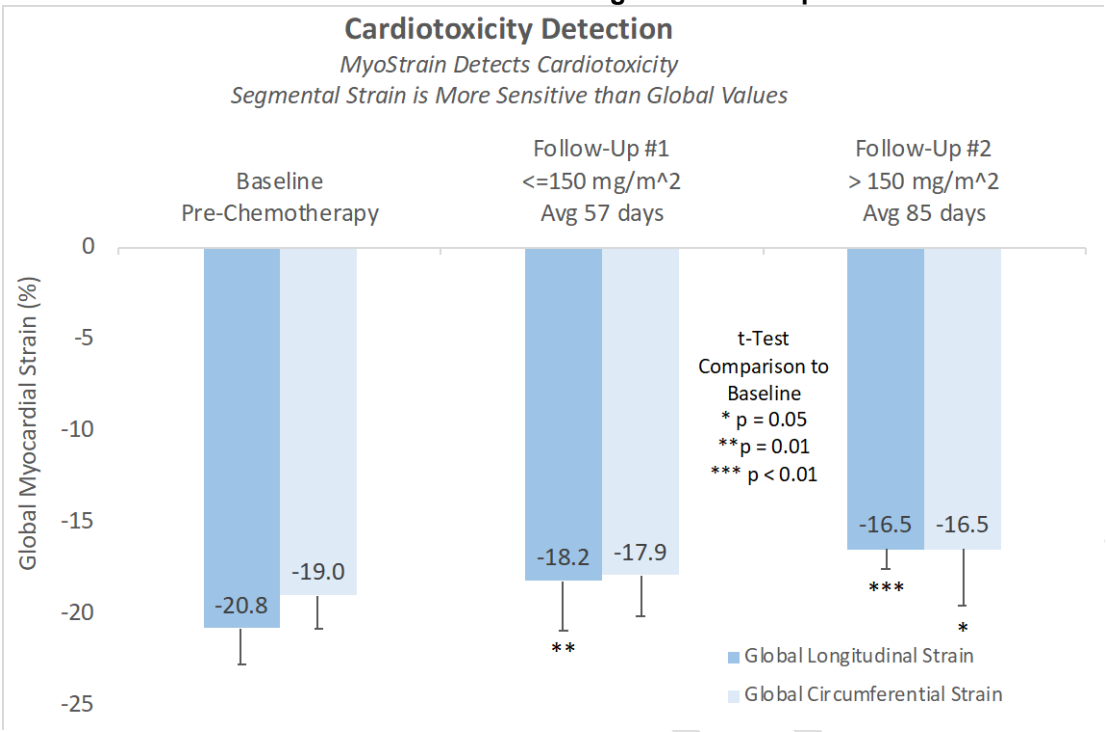
- **Baseline Echocardiography Data**

Baseline Echocardiography Data	Average ± St Dev
LVEF (%)	63.9 ± 5.8
LVEDV Index (ml/m^2)	47.7 ± 10.1
LVESV Index (ml/m^2)	17.3 ± 6.4
Stroke Volume Index (ml/m^2)	30.3 ± 5.1
GLS (%)	-26.5 ± 14.6
E/E'	8.8 ± 2.0
# Pts with Poor Acoustic Window: 4/14 (29%)	

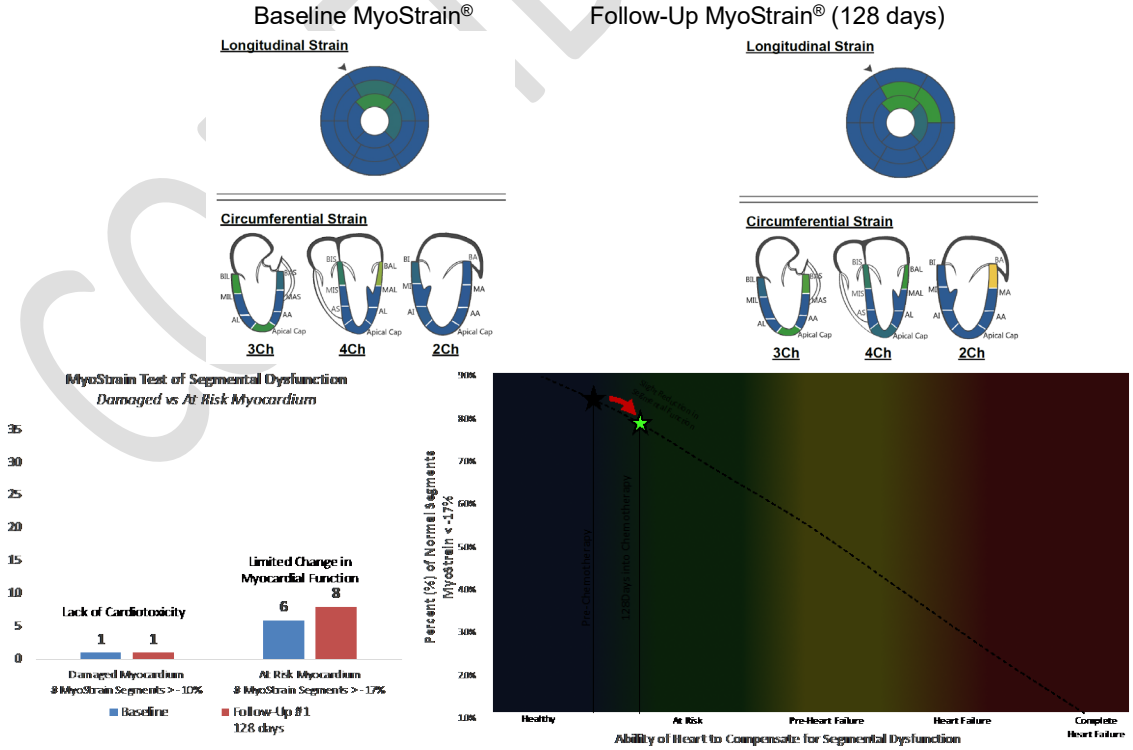
- **Interim Results of Segmental Dysfunction and Global Measures Throughout Follow-up**



- **Interim Results of Global Strain Evolution Throughout Follow-up**

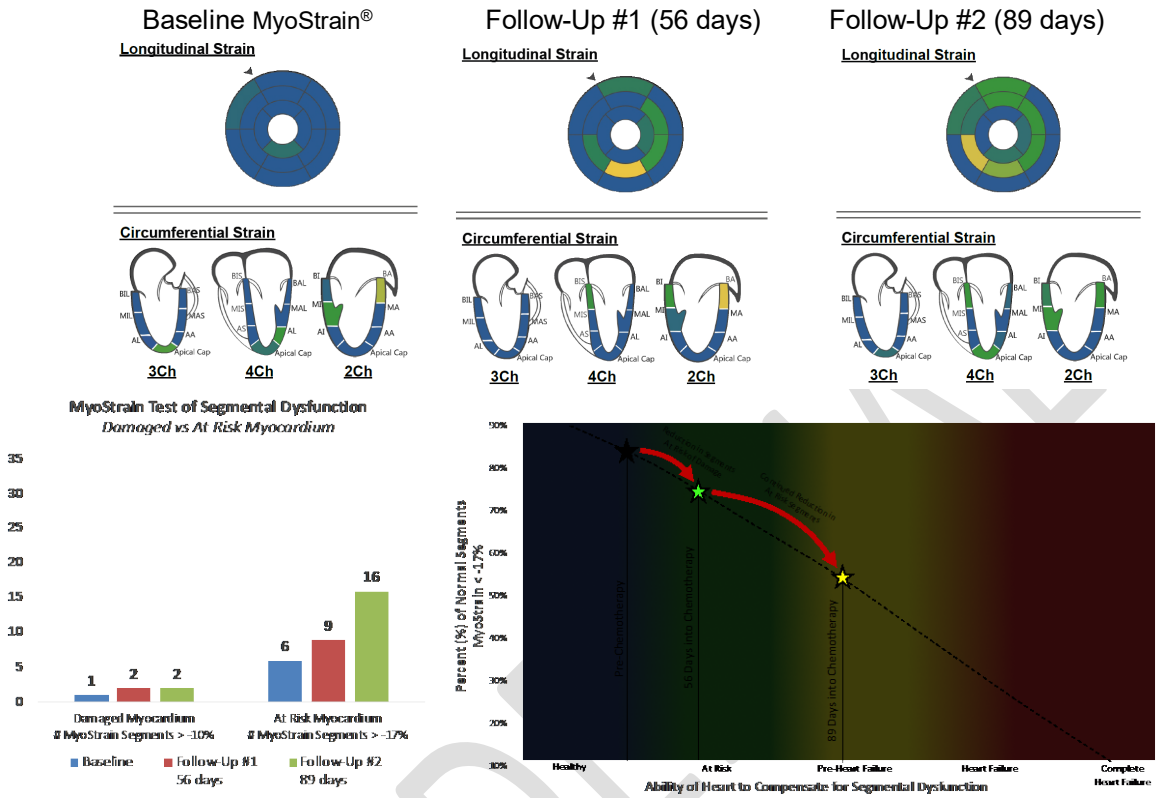


- **Example of Low Risk Patient Not Experiencing Cardiotoxicity.**
A 50 year female with breast cancer did not show substantial dysfunction after 360 mg/m^2 of epirubicin at a follow-up of 128 days. The patient had LVEF of 57% at baseline and 61% after 128 days of chemotherapy. The GLS and GCS did not decrease significantly from baseline to follow-up (GLS:-22% vs -20% and GCS: -20% vs -19%). Segmental dysfunction also did not substantially change throughout follow-up representing adequate myocardial health during cancer treatment.

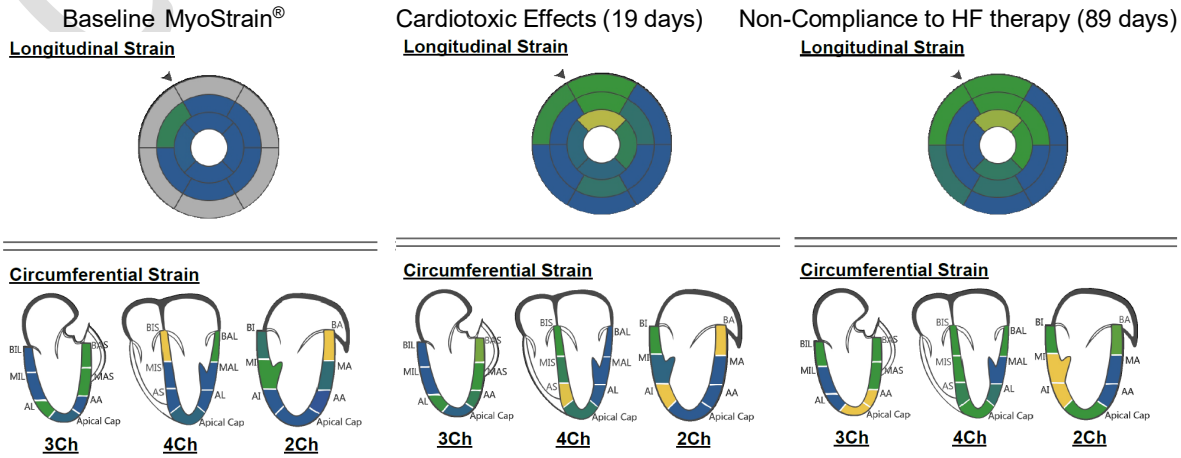


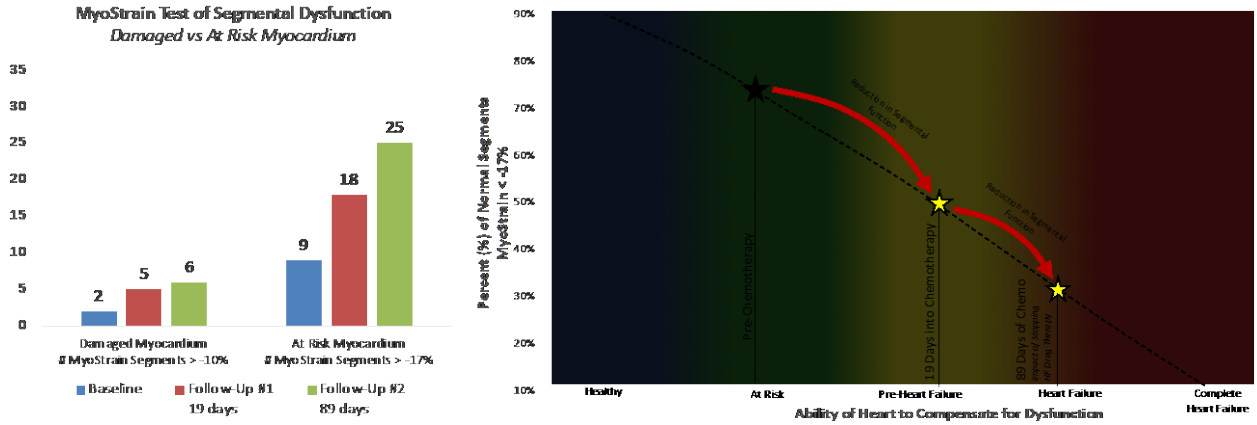
- **Example of Low Risk patient showing progressive decline thereby increasing risk of developing cardiotoxicity during continued treatment.**
A 46 year female treated for breast cancer observed progressive decline throughout 89 days of follow-up with a total of 360 mg/m^2 epirubicin and 160 mg/m^2 Paclitaxel. The patients LVEF fluctuated but

remained in the normal range at baseline, 56 days, and 89 days of follow-up (68%, 56%, and 66%). GLS and GCS showed gradual decline throughout follow-up (GLS -22% vs -19% vs -17% and GCS: -20% vs -21% vs -19%). Segmental dysfunction showed progressive worsening throughout follow-up indicating the reduced ability of the heart to compensate for gradual myocardial damage due to cardiotoxic effects of chemotherapy.

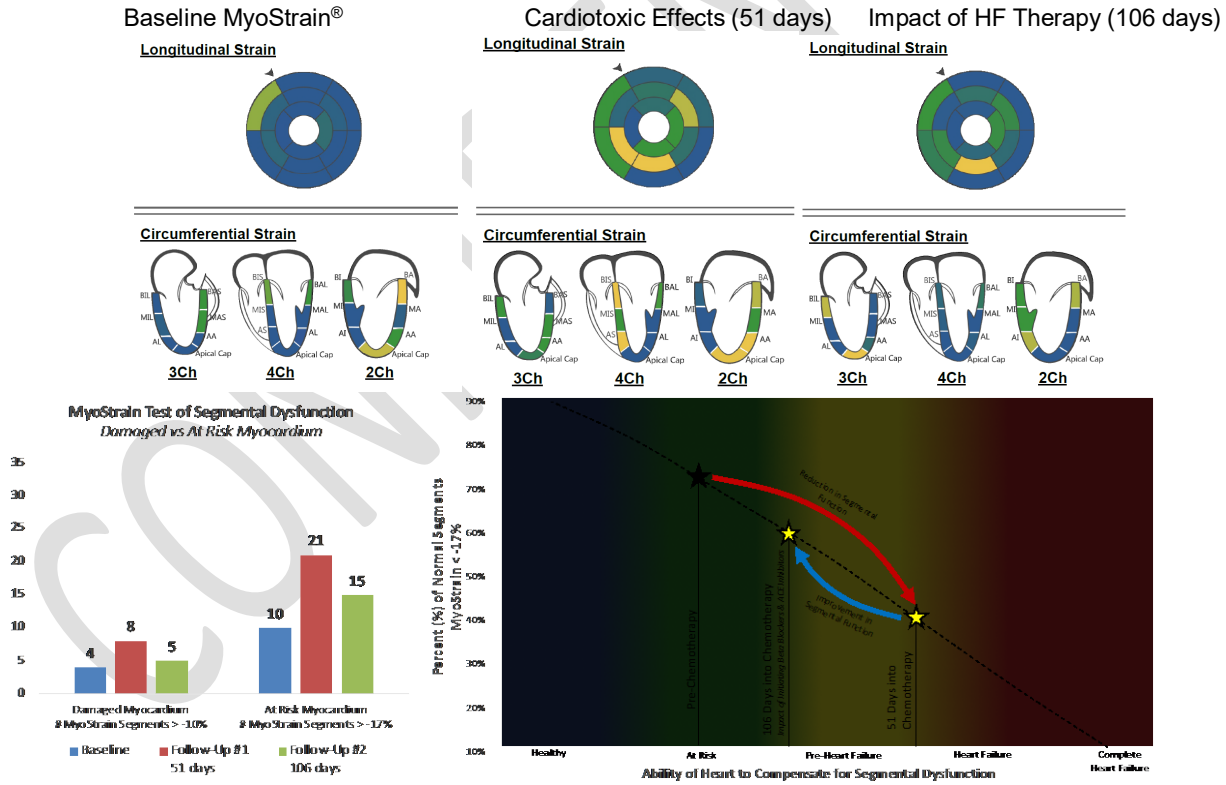


- **Example of a Medium Risk patient observing cardiotoxic effects and showing non-compliance with preventative therapy.**
  A 66 year female treated for lymphoma observed substantial segmental myocardial dysfunction after administration of 150 mg/m^2 doxorubicin at a follow-up of 19 days. The patient was not compliant with the prescribed Heart Failure therapy and observed continued progression of myocardial dysfunction at 89 days and cumulative dose of 300 mg/m^2 of doxorubicin and 375 mg/m^2 of rituximab. Subsequently, the patient was urged to maintain compliance to address the cardiotoxic effects of chemotherapy. The patient's LVEF reduced well after segmental dysfunction identified the risk and worsening of myocardial health, measuring 64% at baseline, 60% at 19 days when MyoStrain® detected worsening dysfunction, and finally reducing to 45% at 89 days since the patient was not compliant with heart failure therapy. However, GLS and GCS continued to decrease significantly from baseline throughout follow-up (GLS:-22.8% vs -16.9% vs -16.3% and GCS: -17.9% vs -16.3% vs -12.3%). Segmental dysfunction demonstrated worsening function throughout follow-up providing a sensitive measure to non-compliance of HF therapy.





- **Example of a High Risk patient observing reversible cardiotoxic effects.**
  A 59 year female treated for Hodgkin lymphoma with doxorubicin observed substantial segmental myocardial dysfunction after administration of 70 mg/m^2 at a follow-up of 51 days. The patient was treated with angiotensin converting enzyme inhibitors (ACE-I)and beta blockers that improved function while maintaining chemotherapy with a cumulative dose of 140 mg/m^2 (follow-up of 106 days). The patient maintained an LVEF around 58% throughout 106 days of chemotherapy. However, GLS and GCS decreased significantly from baseline to first follow-up before improving upon prescription of preventative heart failure therapy (GLS:-20.5% vs -15.1% vs -17.7% and GCS: -18.3% vs -14.9% vs -16.6%). Segmental dysfunction also demonstrated worsening function until heart failure therapy was employed at which time heart function improved.



- **Summary**
  The PROACT Pilot study showed the ability of MyoStrain® to quantify the progressive changes in segmental and global myocardial health during cancer treatment to detect subclinical cardiotoxic effects of chemotherapy and/or targeted treatment. In this pilot study, serial MyoStrain® scans also enabled patient management to identify patients in need of proactive cardiac protection therapy while monitoring the impact including compliance of such therapy. The ability to define risk assessment based on segmental dysfunction allows identification of patients at risk of developing cardiotoxicity to monitor those predisposed to developing new or worsening heart failure. The findings in this pilot study provide further evidence for the inclusion criteria and performance criteria of the PROACT study.

2.4. Risk Analysis and Risk Assessment

The MSI SENC MyoStrain® software has been tested and approved following ISO 14971 (Medical Devices – Application of Risk Management to Medical Devices).

Detailed risk assessments have been done by Myocardial Solutions, Inc. throughout the software development. The company routinely performs management review that include analysis of device performance, change control (design, process, labeling), and corrective and preventative action for the product.

Myocardial Solutions' risk assessment has been completed and clinical risks have been reduced as far as possible by device design, labeling, and training protocols for intended users. There are no unacceptable residual clinical risks based on the risk/benefit reviews.

3. OBJECTIVES

The primary objectives of this study are:

1. to robustly quantify myocardial function in cancer patients scheduled to receive anti-cancer therapy
2. to determine the ability of MyoStrain® testing to detect subclinical cardiac dysfunction compared to standard cardiac imaging
3. to determine the impact of MyoStrain® imaging on medical management of cardiotoxicity through early detection of at risk patients.

4. PROJECT DESCRIPTION

This study evaluates the impact of medical management of cardiotoxicity through early detection of at risk patients and management of with heart failure therapy to restore myocardial function.

SENC MyoStrain® testing will quantify changes in myocardial function at pre-defined intervals to detect the progression of cardiotoxic effects of chemotherapy and/or targeted treatment. Cancer treatment regimens such as anthracyclines, trastuzumab, taxanes, other agents, or combination of drugs, with or without concomitant Radiotherapy, have been shown to cause cardiotoxicity leading to heart failure. [22] [23]

MRI strain testing (SENC or HARP) has been shown to detect cardiotoxicity before systemic changes occur. MRI strain has been shown to detect abnormal myocardial function in cancer patients treated with high-dose anthracycline chemotherapy despite normal systolic function by traditional measures. [24] [25] Clinical utility of SENC strain testing is to evaluate risk of heart failure, immediate or delayed, for chemotherapy to reduce adverse cardiac events in cancer patients treated with anthracyclines or other drug therapy known to cause cardiotoxicity.

5. STUDY DESIGN

5.1. Summary Protocol

Patients with any type of cancer scheduled to receive anti-cancer therapy with or without concomitant radiotherapy and enrolled in the SURVIVE Registry will be evaluated based on baseline MyoStrain® segmental dysfunction risk profile. After consenting to the PROACT study, patients will undergo a baseline MRI to determine their risk stratification for the study. This baseline MyoStrain® MRI must demonstrate 2 or more segments measuring >-10% or 9 or more segments >-17% for entrance into the study.

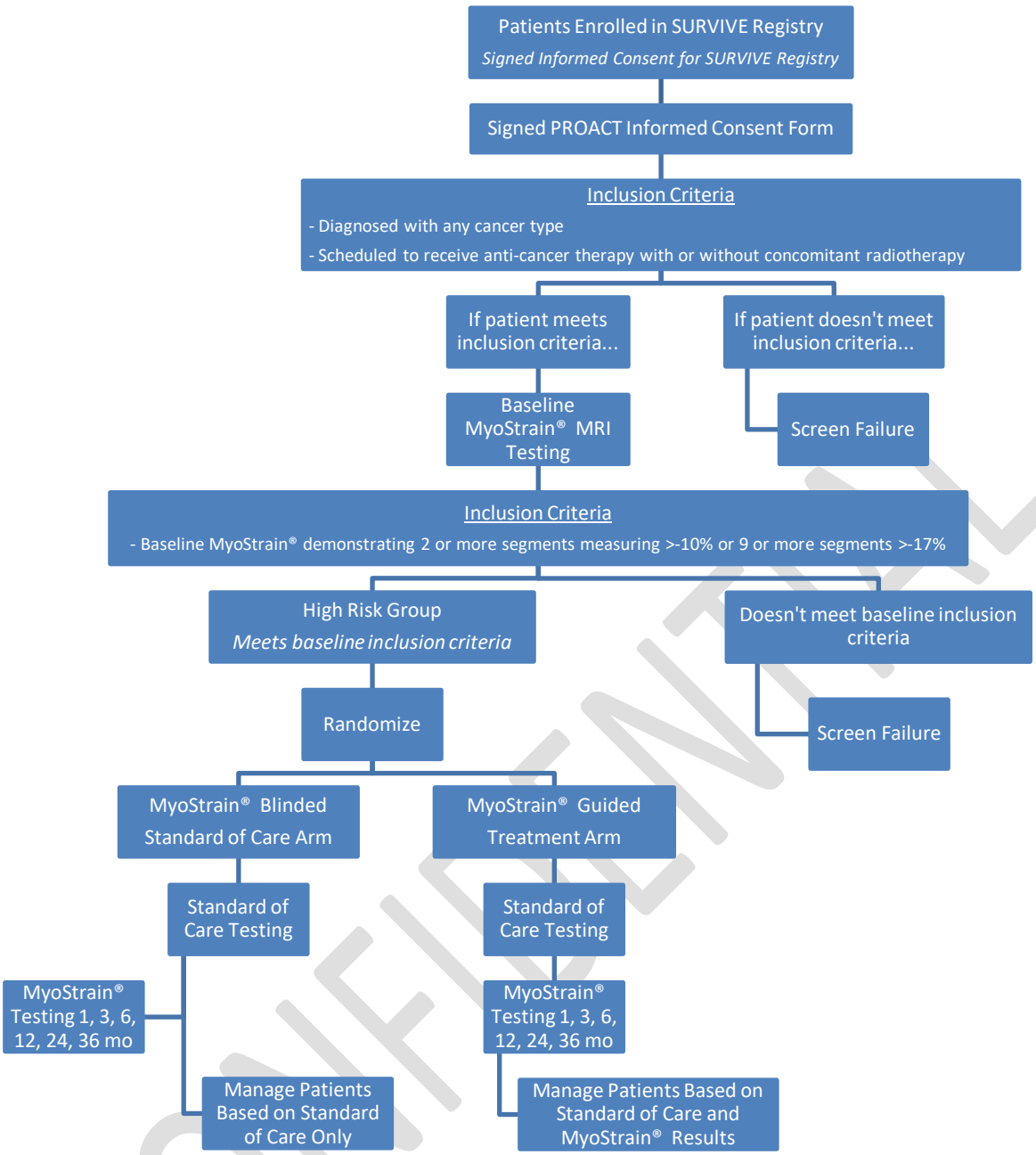
Eligible patients will then be randomized 1:1 into the MyoStrain® guided treatment arm versus the Myostrain® blinded observational arm, as shown in Figure 2. The treatment arm will guide patient management by augmenting standard of care with serial MyoStrain® monitoring of the impact of cancer therapy on myocardial function by providing physicians with MyoStrain® values, in addition to LVEF, LVEDV, and LVESV. In the

observational arm, physicians will only be provided with LVEF, LVEDV, and LVESV, which are clinical measurements. The standard of care assessments by cardiac MRI, will not include MyoStrain® assessments.

In order to obtain the MyoStrain® values, MRI images obtained will be uploaded de-identified to Myocardial Solutions, Inc. After the baseline scan, Myocardial Solutions, Inc. will inform research staff whether the patient met criteria for continued follow up in the study. At that time, the patient will be randomized to one of the two arms, as previously described, and Myocardial Solutions, Inc. will be made aware of the randomization result. If randomized to the blinded observational arm, no results from any cardiac MRI obtained for the study will be provided to physicians from Myocardial Solutions, Inc. If randomized to the MyoStrain® guided treatment arm, MyoStrain® results and LVEF, LVEDV, and LVESV will be provided for all cardiac MRI's obtained in the study to the physicians. Sites will also send Myocardial Solutions, Inc. de-identified information about the patients' medical history (i.e. comorbidities, past/current medications, etc.).

Patient's will continue to undergo MyoStrain® MRI testing, regardless of study arm, at 1 month (± 2 weeks), 3 months (± 2 weeks), 6 months (± 2 weeks), 12 months (± 30 days), 24 months (± 30 days), and 36 months (± 30 days) after the baseline visit. In addition to the MyoStrain® testing, patients will also be asked to complete a brief patient satisfaction questionnaire at each PROACT time point. Patient's will already be completing the EQ-5D Questionnaire and the Cardiovascular Risk Assessment Questionnaire as part of the SURVIVE Registry protocol at the baseline, 6 month, 12 month, 24 month, and 36 month time points.

In addition to Myocardial Solutions, Inc. reviewing the cardiac MRI images, due to the multi-departmental nature of this study, sites may also choose to obtain a clinical read on the research cardiac MR images obtained on the short axis, which are the same images that would be obtained in a clinical MRI, and provide only the LVEF, LVEDV, and LVESV for all subjects, regardless of randomization arm, and those values may be uploaded to the patients' medical record, if permitted. Doing so would then allow patients' oncology team access to this information in lieu of obtaining additional testing (i.e. clinical cardiac MRI's, echocardiograms, etc.) to obtain this same information.



EXAMPLE OF GENERAL PRINCIPLES FOR CLINICAL DECISIONS WITH MYOSTRAIN® RESULTS:

- Worsening segment abnormalities, consider cardio-protective therapies.
- Advise oncology about developing toxicities.
- Enhance patient education (symptom awareness).

Figure 2 – Study Flow Diagram

PROACT Schedule of Events	Baseline	1 Month (±2 weeks)	3 Month (±2 weeks)	6 Month (±2 weeks)	12 month (±30 days)	24 month (±30 days)	36 month (±30 days)
PROACT Informed Consent	✓						
Inclusion/Exclusion Criteria Confirmation	✓						
MyoStrain® MRI Testing	✓	✓	✓	✓	✓	✓	✓
Randomization	✓						
Patient Satisfaction Questionnaire	✓	✓	✓	✓	✓	✓	✓

5.2. MyoStrain® Testing Methodology

System setup and testing methodology will follow the Myocardial Solutions SENC User's Manual 4.1. The SENC MyoStrain® Test procedure is a quick and simple analysis which will require only one series of images. The importation of the images from the scanner and organization of these images is mostly automated and requires very minimal interaction to function correctly. The workflow of the SENC MyoStrain® test requires only one scan and analysis phase allowing the complete scan to be completed with 6 heartbeats after imaging planning without breath-holds.

1. **Use Preview mode for discovery and planning**
   - Before the actual analysis begins, the operator will use Preview mode to perform image planning and ensure the scanner is looking in the correct location and the myocardium is being imaged properly.
   - After using Preview mode, the operator will switch the mode to Strain before acquiring more images or beginning the exam by clicking the Strain button found above the Report section

2. **Select one slice from the Image List**

3. **Identify view and locate end-systole**

4. **Draw epicardial and endocardial contours on the myocardium**
   - To ensure accurate analysis of any view of the heart, the operator will draw a contoured mesh around the heart tissue. The mesh will quantify the entire LV of the current view and automatically segment the heart using the standard AHA model. This is done by drawing a contour on both the epicardial and endocardial edges of the left ventricle. The mesh application should be performed on each slice/view available.
   - NOTE: When computing the strain after segmenting the heart with a mesh, the strain measurements are restricted within the mesh.

5. **Repeat steps 2-4 for each image in Image List**

6. **After all images have been analyzed, complete the report and Export to PDF**
   - The Report Page automatically composes a report from the various sources of information that are obtained during the analysis. This report can then be uploaded, exported as a PDF document, or printed out for review.

During the SENC MyoStrain® Test analysis, each mesh applied to the dataset will populate the appropriate model in the Measures section. The color legend in Figure 3 provides a basic guide to the meaning of each color. The coloring shown demarcates specific regions validated in published literature based on levels of myocardial function. Normokinetic defines strain < -17% while Akinetic defines strain > -10%. The numeric strain values for each segment and global measurements will also be displayed on the report. Alternative coloring schemes may be utilized depending on operator preference.

Figure 3: Color Legend for Strain Test

The Measures section SENC MyoStrain® exams will display resting strain, as well as global circumferential and longitudinal strain as shown in Figure 4.

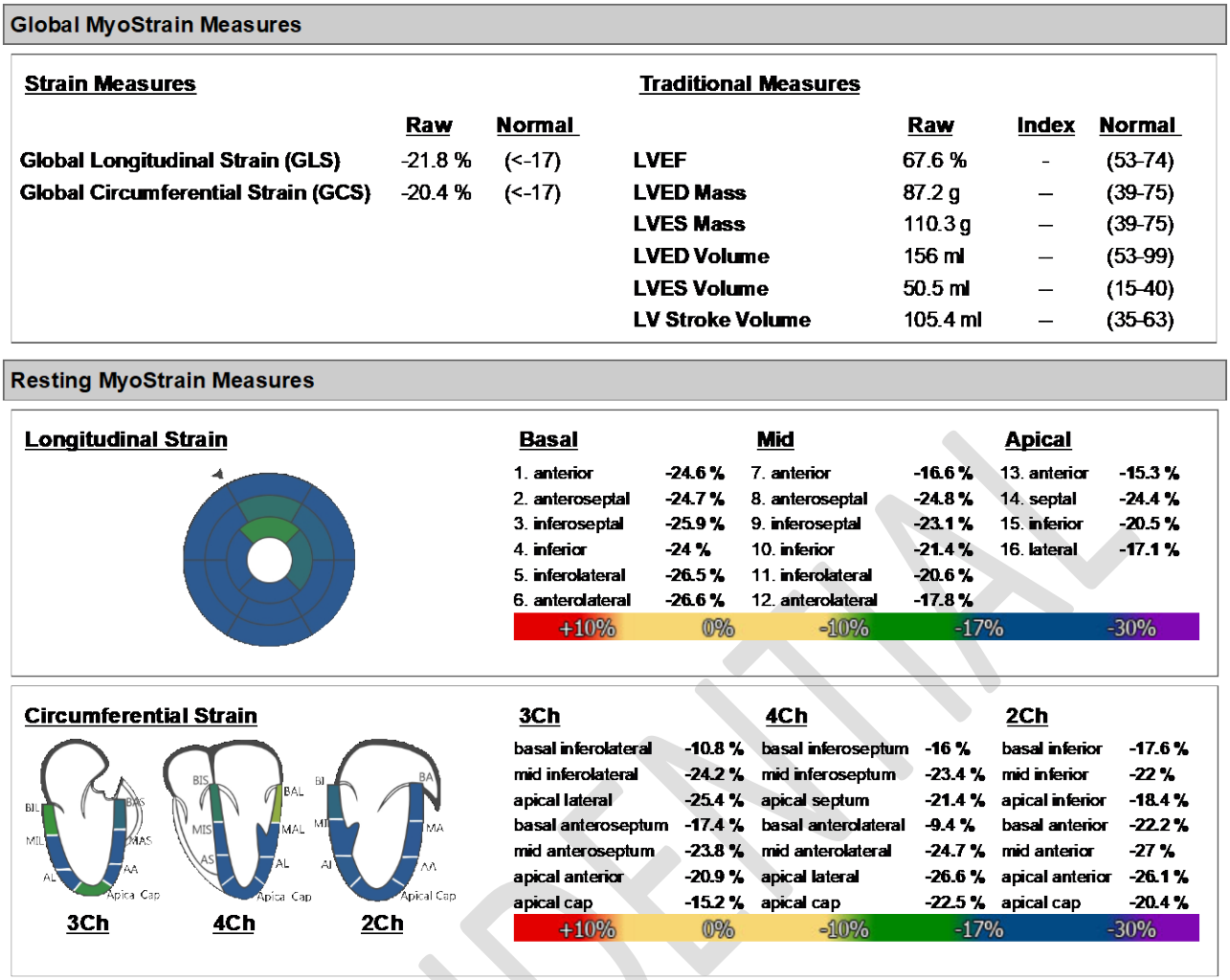


Figure 4: Example Strain exam with 6 views quantified

5.3. Study Population

Subjects enrolled in the SURVIVE Registry and scheduled to undergo chemotherapy or targeted cancer treatment will be consented for possible inclusion in PROACT. Then the patient will be evaluated with a baseline MyoStrain® test to determine whether the patient exhibits moderate or high risk of developing cardiotoxicity. As a minimum, the inclusion and exclusion criteria listed below will apply.

5.4. Inclusion Criteria

1) Participant in the SURVIVE registry
2) Signed consent form for PROACT
3) Histological diagnosis of any cancer type (patients with treated and clinically stable brain metastasis are acceptable)
4) Scheduled to receive anti-cancer therapy (radiation therapy is permitted)

5.5. Exclusion Criteria

5) Contraindication to magnetic resonance imaging (MRI)
6) Unable to comply with study investigations (in the judgment of the investigator)
7) Life expectancy less than 1 year

Note: If a patient develops a temporary contraindication (e.g. temporary tissue expanders in breast cancer patients) after the baseline MRI, follow up MRIs will be discontinued for safety for the duration in which the patient has a contraindication. However, once the patient is no longer contraindicated to receiving MRIs, the study schedule may resume with their next scheduled MRI time point from date of enrollment. Therefore, some time points may be skipped during the patient's enrollment in the study.

Also, if a patient needs a repeat MRI at any time point for any reason (i.e. panic attack during the MRI causing them to not be able to continue, unreadable images, etc.), we may repeat the MRI as long as the patient is willing.

5.6. Duration of the study for the subject

Based on an enrollment of 40 evaluable patients (a subset of the approximately 700 SURVIVE Registry patients enrolled annually across all SURVIVE participating sites) who demonstrate moderate to high risk of cardiotoxic effects during cardio-oncology treatment due to observed segmental dysfunction at baseline, it is anticipated that all subjects will be enrolled within 12 months after study initiation. The study will end when the last enrolled subject completes the 36-month follow-up, data is analyzed and reports are written. Therefore, study duration is anticipated to be approximately 54 months.

5.7. Sample size

40 evaluable patients will be randomized 1:1 to the MyoStrain® imaging guided arm versus the standard of care arm.

5.8. Enrollment

Subjects are considered to be enrolled in the study after they have signed the IRB approved PROACT informed consent form. No investigational tests will be performed before this moment.

6. INFORMED CONSENT

6.1. Consent for Study Participation

All subjects recruited for study participation must meet all study enrollment inclusion/exclusion criteria prior to being enrolled in the study. Once compliance with study inclusion/exclusion criteria is confirmed and the Investigator has determined that a subject is potentially eligible for study participation, the subject may be asked to participate in the study. Informed consent must be obtained from all subjects prior to study participation. The Informed Consent must be approved by the Institutional Review Board (IRB)/Ethics Committee (EC) overseeing the conduct of this study. Each original signed informed consent will be retained in the subject's study records and a copy of the consent should be provided to the subject.

6.2. Subject withdrawal

Subjects can withdraw informed consent at any time during the study. Subjects who withdraw informed consent will not be replaced and the data will not be analyzed (per protocol analysis, see section "statistical considerations"). Subjects discontinuing participation in the study upon written notification before completion of the predefined follow-up will have their data (baseline and interim follow-up intervals) imputed from analysis.

7. RISK / BENEFIT ASSESSMENT

7.1. Risks

The SENC MyoStrain® software with the associated pulse sequence patch is a noninvasive imaging technology. There is minimal direct physical risk for imaged subjects as it is an MRI procedure that does not require any invasive intervention or injections. As such the risks are limited to those typical for conventional MRI exams. Subjects will be evaluated for potential contraindications to MRI imaging. Considering image acquisition is very fast (< 5 min) reducing time within the magnetic bore and patients do not need to hold their breath during image acquisition, risks of claustrophobia or anxiety may actually be reduced compared to traditional MRI tests.

7.2. Benefits

The results of the strain analysis provide quantitative assessment of regional function. These measurements will be utilized as observational analysis. Physicians will make clinical decisions using all available clinical information and cardiac test results that are available.

8. ONCORE REGISTRATION PROCEDURES

Patients must not start any protocol intervention prior to registration through the Siteman Cancer Center.

The following steps must be taken in order to register patients to this study:

1. Confirmation of patient eligibility by site PI
2. Consent of patient to PROACT study
3. Confirmation of patient eligibility by Washington University
4. Assignment of Participant ID
5. Registration of participant in the Siteman Cancer Center OnCore database

Once the patient has been entered into the Siteman Cancer Center OnCore database, the coordinating center's coordinator will forward verification of enrollment and the subject ID.

8.1. Confirmation of Patient Eligibility by WUSTL Prior to Registration

Confirm patient eligibility by collecting the information listed below and scanning and emailing it to the coordinating center's coordinator at least one business day prior to the patient's baseline MRI scan:

1. Your name and contact information (telephone number, fax number, and email address)
2. Your site PI's name, the registering investigator's name, and your institution name
3. Patient's race, sex, and DOB
4. Three letters (or two letters and dash) for the patient's initials
5. Currently approved protocol version date
6. Copy of signed consent form
7. Completed eligibility checklist, signed and dated by a member of the study team
8. Copy of appropriate source documentation confirming patient eligibility

The coordinating center will email the participating site with verification of eligibility of the patient within 1 business day. Once verification of eligibility has been received, the patient will be registered into OnCore and the patient may undergo the baseline MRI scan.

8.2. Patient Registration in the Siteman Cancer Center OnCore Database

Registrations may be submitted Monday through Friday between 8am and 5pm CST. Urgent late afternoon or early morning enrollments should be planned in advance and coordinated with the Washington University research coordinator. Registration will be confirmed by the research coordinator or his/her delegate by email within 1 business day. Verification of eligibility and registration should be retained in the participant's study chart.

All patients at all sites must be registered through the Siteman Cancer Center OnCore database at Washington University after the patient has been consented, prior to the baseline MRI scan.

8.3. Assignment of Participant ID

Each patient will be identified with a unique Participant ID for this study. The Participant ID will be based on the patient's Participant ID in the SURVIVE Registry, as well as the patient's enrollment number in the PROACT study. All data will be recorded with this Participant ID on the appropriate CRFs.

9. ADVERSE EVENTS AND REPORTING REQUIREMENTS

Only adverse events in relation to the study procedures will be documented and reported. These include adverse events occurring from the MRI scanner, SENC MyoStrain® Testing Software, or breach of confidentiality. Adverse events in relation to cancer diagnosis will not be recorded or reported. Recording of adverse events must be documented by the Participating Sites and entered into REDCap on a continuous basis.

9.1. Adverse Event Definitions

Term	Definition
Adverse Event (AE)	An unfavorable medical occurrence in a human subject including any abnormal sign, symptom, or disease.
Serious Adverse Event (SAE)	An adverse experience occurring that results in any of the following outcomes: a. Death b. A life-threatening adverse experience

	c. Inpatient hospitalization or prolongation of existing hospitalization d. A persistent or significant disability/incapacity (i.e. a substantial disruption of a person's ability to conduct normal life functions) e. A congenital anomaly/birth defect f. Any other experience which, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above
Life-Threatening	An adverse experience that places the subject (in the view of the investigator) at immediate risk of death from the reaction as it occurred, i.e. it does not include a reaction that, had I occurred in a more severe form, might have caused death.

9.2. Attribution, Anticipation, Expectedness, and Grading of AEs

The terms for attribution, expectedness, and severity are defined as follows:

9.2.1. Attribution

Classification	Description
Definitely Related	The adverse event, incident, experience or outcome was definitely caused by the procedures involved in the research.
Probably Related	There is a reasonable probability that the adverse event, incident, experience or outcome may have been caused by the procedures involved in the research.
Possibly Related	There is a reasonable possibility that the adverse event, incident, experience or outcome may have been caused by the procedures involved in the research.
Unlikely Related	The adverse event, incident, experience or outcome was unlikely caused by the procedures involved in the research.
Unrelated	The adverse event, incident, experience or outcome was unrelated to the procedures involved in the research.

9.2.2. Anticipation

Classification	Description
Anticipated	Any incident, experience, or outcome that is anticipated to occur due to the research (i.e. procedures, investigational medication, etc.).
Unanticipated	Any incident, experience, or outcome that meets all of the following criteria: a. unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied; b. related or possibly related to a subject's participation in the research; and c. suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) related to the research than was previously known or recognized.

9.2.3. Expectedness

Classification	Description
Expected	Any adverse event that is a known or foreseeable risk associated with the procedures involved in the research or is an expected natural progression of any underlying disease, disorder, or condition.
Unexpected	Any adverse event occurring in one or more subjects in a research protocol, the nature, severity, or frequency of which is not consistent with either: a. the known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in (a) the protocol–related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts; or

	b. the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.

9.2.4. Grading

Grading refers to the severity of the adverse event. All adverse events will be graded using the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The CTCAE displays grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Classification	Description
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL (preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.).
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL (bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

For AE specific grading, please visit the following website to download a copy of the CTCAE version 5.0:
https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

9.3. Noncompliance and Exceptions

Term	Definition
Noncompliance	Failure to follow an applicable regulation or institutional policies that govern human subjects research or failure to follow the determinations of the IRB. Noncompliance may occur due to lack of knowledge or due to deliberate choice to ignore regulations, institutional policiers, or determinations of the IRB.
Serious Noncompliance	Noncompliance that materially increases risks, that results in substantial harm to subjects or others, or that materially comprises the rights or welfare of participants.
Protocol Exceptions	A planned deviation from the approved protocol that are under the research team's control. Exceptions apply only to a single participant or a singular situation. Washington University central IRB pre-approval of all protocol exceptions must be obtained prior to the event for both the coordinating center and all participating sites. Participating sites must also follow their local IRB's guidelines for any submission that needs to be made to their local IRB.

9.4. Reporting Requirements

The entities providing oversight of safety and compliance with the protocol require reporting as outlined below. The Washington University Human Research Protection Office (HRPO) requires that all events meeting the definition of unanticipated problem or serious noncompliance be reported as outlined.

9.4.1. Reporting to the Human Research Protection Office (HRPO) at Washington University

The PI is required to promptly notify the IRB of the following events:

- Any unanticipated problems involving risks to participants or others which occur at WU or any BJH or SLCH institution that impacts participants or the conduct of the study.
- Noncompliance with federal regulations or the requirements or determinations of the IRB.
- Receipt of new information that may impact the willingness of participants to participate or continue participation in the research study.

These events must be reported to the IRB within **10 working days** of the occurrence of the event or notification to the PI of the event. The death of a research participant that qualifies as a reportable event should be reported within **1 working day** of the occurrence of the event or notification to the PI of the event.

9.4.2. Reporting to the Quality Assurance and Safety Monitoring Committee (QASMC) at Washington University

The PI is required to notify the QASMC of any unanticipated problem occurring at WU or any BJH or SLCH institution that has been reported to and acknowledged by HRPO as reportable. Unanticipated problems reported to HRPO and withdrawn during the review process need not be reported to QASMC.

QASMC must be notified within **10 days of receipt** of IRB acknowledgement via email to a QASMC auditor.

9.4.3. Reporting Requirements for Participating Sites

The research team at each participating site is required to promptly notify the Washington University PI and research coordinator of all reportable events within **1 working day** of the occurrence of the event or notification of the participating site's PI of the event. This notification may take place via email if there is not yet enough information for a formal written report. A formal written report must be sent to the Washington University PI and research coordinator within **10 working days** of the occurrence of the event or notification of the secondary site's PI of the event. The death of a research participant that qualifies as a reportable event should be reported within **1 working day** of the occurrence of the event or notification of the participating site's PI of the event.

The research team at a participating site is responsible for following its site's guidelines for reporting applicable events to its site's IRB according to its own institutional guidelines. Since sites will be relying on Washington University's IRB, any reportable event will also be submitted to Washington University's IRB for review.

9.4.4. Reporting to Participating Sites

The Washington University PI (or designee) will notify the research team at each participating site of all reportable events that have occurred at other sites within **10 working days** of the occurrence of the event or notification of the PI of the event. This includes events that take place both at Washington University and at other participating sites, if applicable.

9.4.5. Reporting to MyoCardial Solutions

The following adverse events will be reported to MyoCardial Solutions within **10 working days** of the occurrence of the event or notification of the PI of the event at either Washington University or any participating site unless the event occurs in a death, in which case it will be reported within **1 working day**:

Term	Description
Device Related Adverse Event (DRAE)	An adverse event will be considered to be related to the device if it results from the use or presence of the MRI Scanner, or the performance of any component of the MRI Scanner.
Unanticipated Adverse Device Effect (UADE)	A device or procedure related adverse effect will be considered unanticipated if it is not identified in the MRI Scanner or SENC MyoStrain® Testing Software operator manuals or instructions for use.

9.4.6. Timeframe for Reporting Required Events

Adverse events will be tracked from time of consent to the last study visit. For the purposes of this protocol, adverse events collected and documented on CRFs include adverse events occurring from the MRI scanner, SENC MyoStrain® Testing Software, or breach of confidentiality.

All incidences of noncompliance and protocol exceptions will be tracked from the time of IRB approval, at the coordinating center, or site initiation at the participating centers, until the close of the study.

For more information on adverse event definitions and classifications and reporting requirements, please visit: https://www.hhs.gov/ohrp/regulations-and-policy/guidance/reviewing-unanticipated-problems/index.html

10. DATA SAFETY AND MONITORING

10.1.1. Data Monitoring by MyoCardial Solutions

Monitoring of the research is the responsibility of the Principal Investigator at each participating site. The participating sites and Myocardial Solutions will meet on regular basis to discuss the progress of the research and the efficiency of the PROACT study.

10.1.2. Data Monitoring by Coordinating Sites

The data consist of information obtained from MyoCardial Solutions, Inc. MyoStrain® software. Data will be stored in two places: 1) a WUSTL REDCap database and 2) all original paper copies will be stored in a locked cabinet behind a locked door at each participating site. Moreover, only the Research Coordinator or designated study staff will have keys to the locked cabinet. Only the designated study staff will have access to any resources with identifying information in REDCap. An important REDCap feature to note is that the access to study data is limited to those assigned access (i.e. Key Study Personnel [KSP]).

Data and regulatory documents from all participating sites will be reviewed by the Washington University Quality Assurance and Safety Monitoring Committee (QASMC) every 6 months. For participating sites added on after study initiation, the first review for that site will take place during the next scheduled QASMC review, which may occur prior to 6 months after site initiation. Because all monitoring will take place remotely, uploads of source documentation, including consent forms with signatures, either to REDCap and/or WUSTL Box will be mandatory for participating sites. In addition, QASMC may request access to participating sites' electronic medical record, if the site's institution allows such access.

Data and regulatory document monitoring will also be conducted by the coordinating center's research coordinators and will consist of data checks, both electronic and manual. Every 6 months prior to QASMC review, data entered into the REDCap database will be reviewed for accuracy by designated study staff at the coordinating center. As with QASMC audits, for participating sites added on after study initiation, the first review for that site will take place during the next scheduled data review. Uploaded source documentation, including consent forms with signatures, by participating sites will also be reviewed for inconsistent data. If there are inconsistencies or missing values, queries will be issued to the participating sites and they will refer to the subject's records to correct the aberration. Participating sites are expected to enter data into REDCap within 14 business days of a study visit. Sites that appear to have significant delays between the time of enrollment/study visits and data entry will be contacted by the coordinating center. Participating sites are also expected to respond to any REDCap queries within 1 month of issuance. Sites that appear to have a significant amount of REDCap queries will be contacted by the coordinating center. At each interval, the coordinating center will note the number of participants accrued to date as well as the number of participants accrued for that 6 months interval.

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

10.1.3. Data Safety and Monitoring Committee

In compliance with the Washington University Institutional Data and Safety Monitoring Plan, the Principal Investigator will provide a Data and Safety Monitoring (DSM) report to the Washington University Quality Assurance and Safety Monitoring Committee (QASAMC) semi-annually beginning six months after accrual has opened (if at least 5 patients have been enrolled) or 1 year after accrual has opened (if fewer than 5 patients have been enrolled at the 6 month mark).

The Principal Investigator will review all patient data at least every 6 months, and provide a semi-annual report to QASMC. The report will include:

- HRPO protocol number, protocol title, Principal Investigator name, and research coordinator name
- Date of initial HRPO approval, date of most recent HRPO approval/revision of consent, date of HRPO expiration, date of most recent QA audit, study status, and phase of study
- History of study including summary of substantive amendments; summary of accrual suspensions including start/stop dates and reason; and summary of protocol exceptions, error, or breach of confidentiality including start/stop dates and reason
- Study-wide target accrual and study-wide actual accrual
- Protocol activation date
- Average rate of accrual observed in Year 1, Year 2, and subsequent years
- Expected accrual end date

- Objectives of protocol with supporting data and list of the number of participants who have met each objective
- Abstract submissions/publications
- Summary of any recent literature that may affect the safety or ethics of the study

11. STATISTICAL CONSIDERATIONS

The data of cardiac features measured will be stored in a WUSTL REDCap-supported database and transformed into a SAS, R, excel, and CSV dataset, so they can be analyzed by our team using SAS, R and PYTHON software packages.

At baseline and any other visit, the standard descriptive statistics will be used to summarize numeric variables, including the number of observed values, mean, standard deviation, median, minimum and maximum values. Summaries of categorical variables will include the number and percentage of observed values, at each level of the categorical variable. Baseline and demographic information will be summarized with standard descriptive statistics.

There will be more than 60 cardiac 3D features measured for each patient (subjects' n=102) resulting from use of MyoStrain SENC software, as shown in the schematic Figure 5. The results will be stratified based on the patient's segmental strain (longitudinal and circumferential) profile with -10% or -17% as the threshold to determine segmental dysfunction and the number of dysfunctional segments delineating patient risk. The patients will be selected at baseline for high cardiovascular risk, which will be important in cancer patients in responding to cardiotoxicity.

Patients will be separated by randomization into two groups. Those of whom the cardiac care will be served with prior knowledge of MyoStrain SENC data as measured in each visit, while the other half, with exception of 4 cardiac measures, they and their doctor will not have knowledge for the full cardiac features, but we will have access to these data also, only at the end of the study.

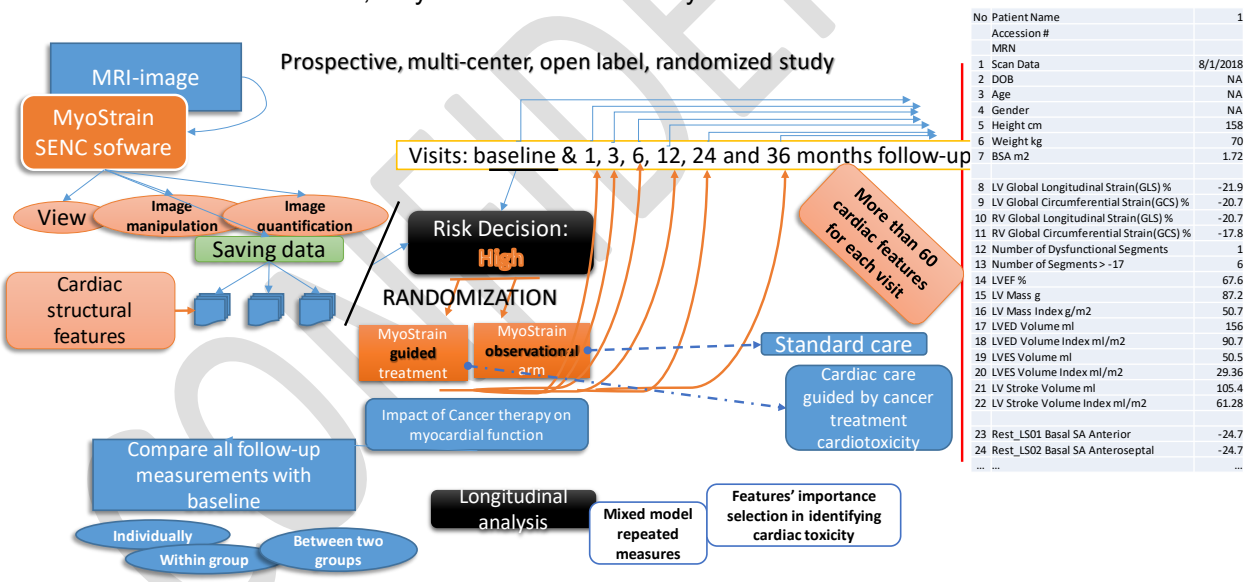


Figure 5: A schematic of measurements and statistical methods to be used for inferring for cardiotoxicity from results of baseline and also at 1, 3, 6, 12, 24 and 36 months' follow-up.

The longitudinal data will be compared for each individual with his/her baseline, to learn and guide each individual's care and to infer the level of cardiotoxicity. The same group's data will be analyzed with the intention in identifying what trends exist among those in the group of MyoStrain SENC software guided treatment. The full cardiac measures for the other group: the observational arm will be available to us at the end of the trial. At that time, we will analyze also the longitudinal cardiac 3D features for this group at the individual levels compared to baseline. In addition, we will analyze the longitudinal data to identify trends for each group, as well as we will compare trends of two groups toward cardiac response to chemotherapy and / or radiology. We will test the cardiotoxicity development i.e. myocardial dysfunction by comparing the efficacy of detecting cardiac dysfunction using standard assessments LVEF, LVESV and LVEDV in time against analyzing all cardiac features collected via MyoStrain (more than 60 of them, Figure 5). Multivariate regression and logistic regression will be used with "stepwise" option to identify significant predictors at standard and guided care features for predicting cardiotoxicity. Furthermore, we will use decision trees for identifying the

importance of MyoStrain cardiac features compared to cardiac toxicity risk prediction based on standard assessment of variables LVEF, LVESV, LVEDV, and LV Stroke Volume Index (LVSVi). Endpoints will be evaluated based on discrete variables of MyoStrain values versus standard assessments. Considering many patients will have a complex management of cardioactive medications as well as cancer treatment regimen, the classification of cardiotoxicity status will be based on a clinical committee to designate whether the patient experienced no cardiotoxicity, functional decline without cardiotoxicity, subclinical cardiotoxicity, or clinical cardiac dysfunction at each exam timepoint. The last analysis will help to identify also any indication for interactions among variables studied. We will implement Intention-To-Treat-analysis, where the analyses of the two groups will be based on the initial treatment assignment in the two randomized groups. If in the follow-up data-points may be missing, we will check if the missing data-points are random and if several covariates can help in imputation of missing. We plan to use MI procedure of SAS Institute for such imputations. The regression will be implemented via GLM, LOGISTIC and MIXED (for statistical analysis of repeated measures) procedures in SAS. For mixed models, a comparison of models will be done via likelihood ratio test and by using the Akaike Information Criterion (AIC) and Schwartz's Bayesian Criterion (SBC). Graphical presentations will be implemented in R via LMER of LME4 mixed modelling build in functions, and specialized software GGPLOT2 in R. Decision (known also as partition) trees will be implemented with SAS-Data Mining software. We will use also PYTHON-scikit machine learning package for testing the performance of partition-trees via random forest. A random forest is a meta estimator that fits a number of decision tree classifiers on various sub-samples of the dataset and use averaging to improve the predictive accuracy and control over-fitting.

Based on pilot data and utilizing only the moderate to high risk group (>2 segments of Myostrain determined segments >17%), the outcome expected would be 12.8 +/- 4.7 dysfunctional segments for the intervention group and 16.8 +/- 7.8 dysfunctional segments for the control group (and using average of 4.7 and 7.8 for the standard deviation for the overall outcome) at 6 months. This same parameter will be followed at the other time points, including 1 year, 2 years, and 3 years, but the primary endpoint will be at 6 months.
With these calculations,102 patients are required to have a 90% chance of detecting, as significant at the 5% level, a decrease in the primary outcome measure from 16.8 in the control group to 12.8 in the experimental group (number of dysfunctional segments (>17%)).

The sensitivity, specificity, and diagnostic accuracy of each reader to detect changes in myocardial function will be determined for quantitative SENC-CMR. Cutoff-values used to calculate sensitivity and specificity of the quantitative SENC parameters were determined using data previously published. The cutoff for the % of MyoStrain segments <= -17% (based on 37 left ventricular segments) in detecting subclinical cardiotoxicity in the PREFECT50 planned interim analysis was 68% and the cutoff for detecting clinical cardiac dysfunction was 49%; a cutoff of 80% differentiates normal cardiac function from patients experiencing functional decline. McNemar's test with continuity correction will be used to compare the diagnostic performance of each of the SENC-CMR cutoff parameters. Additionally, Receiver Operating Characteristic curves as well as Precision Recall curves will be generated to calculate and compare the area under the curves to determine the diagnostic performance of changes in strain parameters and standard assessments. Inter- and intra-observer variability will also be determined for each of the above parameters using intraclass correlation.

12. DATA MANAGEMENT

The coordinating center and primary investigator are responsible for data management. The investigator/clinical coordinator at each participating site will be responsible for completion and timely input of the study data into the WUSTL REDCap database. Data entered will be reviewed to identify inconsistent or missing data and Adverse Events. The Investigator at each participating site is to maintain all source documents as required by the protocol, including SENC MyoStrain® results, supporting medical records, and Informed Consents.

Confidentiality of data shall be observed by all parties involved during the research. The privacy of each subject and confidentiality of his/her information shall be preserved in reports and when publishing any data.

13. DEVICE ACCOUNTABILITY

Records shall be kept to document when the SENC software and pulse sequence patch is received, returned, uninstalled or disposed at the participating sites.

14. STATEMENTS OF COMPLIANCE

This study will be conducted according to good clinical practice guidelines, the Declaration of Helsinki, and the ANSI ISO 14155: clinical investigation for human subjects. Written informed consent for the study will be received from all participants.

15. INVESTIGATOR RESPONSIBILITIES AND OBLIGATIONS

15.1. Investigator Responsibilities

The investigator is responsible for obtaining the initial and continuing review and approval from the authorized IRB/Ethics Committee for the participating site at which the proposed clinical investigation is to be conducted. The Investigator is responsible for ensuring that informed consent is obtained from each study subject prior to the initiation of any study procedures.

15.2. Investigator Records

The Investigator will maintain complete, accurate and current study records, including the following materials:

1) Study Subject Records, including Informed Consent forms, supporting source documents, and CMR image files including MyoStrain® reports;
2) All relevant observations, including records concerning adverse device effects (whether anticipated or unanticipated);
3) Current study protocol and protocol deviation log, with dates and details of any reason for deviations from the protocol that could affect the scientific quality of the study or the rights, safety, or welfare of the subjects;
4) The approved blank Informed Consent form and Case Report Forms (CRFs); and
5) Documentation that the Investigational Plan has been approved by all of the necessary approving authorities.

15.3. Investigator Reports

The Investigator will be responsible for the following reports:

- **Unanticipated Adverse Device Effect:** The Investigator shall report all Unanticipated Adverse Device Effects to the Sponsor and to the reviewing IRB as soon as possible, but no later than 10 working days after the Investigator first learns of the effect. All Unanticipated Adverse Device Effects should be documented by time of onset, a complete description of the event, severity, duration, actions taken and event outcome.
- **Withdrawal of IRB/EC Approval:** The Investigator shall report to the Sponsor within 5 working days if, for any reason, the IRB/Ethics Committee withdraws approval to conduct the investigation. The report will include a complete description of the reason(s) for which approval was withdrawn.
- **Deviations from the Investigational Plan:** The Investigator shall notify the Sponsor and the reviewing IRB of any changes in, or deviations from, the Investigational Plan to protect the life or physical well-being of the Subject in an emergency. Such notice shall be given as soon as possible, but no later than 5 working days after the emergency occurs.
- **Final Report:** The Investigator will submit a final report to the Sponsor and to the IRB/EC within 3 months of termination of the study or termination of that Investigator's participation in the study.

15.4. Financial Disclosure by Clinical Investigators

Pursuant to 21 CFR part 54 and prior to the initiation of the study, each investigator must disclose certain financial arrangements that may exist between that investigator and Myocardial Solutions. This information will be collected from each investigator, maintained in confidential files at Myocardial Solutions and will be available for review by regulatory agencies upon request.

16. REFERENCES

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17. APPENDICES

17.1. Patient Satisfaction Questionnaire

Patient Satisfaction Questionnaire

Completion Date:_____ Participant ID:_____

Visit: ☐ Baseline ☐ 1 month ☐ 3 month ☐ 6 month
☐ 12 month ☐ 24 month ☐ 36 month

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

	Strongly Agree	Agree	Disagree	Strongly Disagree	Not Applicable
It was easy to schedule a convenient appointment.	❒	❒	❒	❒	❒
The staff was courteous and helpful.	❒	❒	❒	❒	❒
The time in the waiting room was reasonable.	❒	❒	❒	❒	❒
I feel burdened participating in this study.	❒	❒	❒	❒	❒
I am glad I am participating in this study.	❒	❒	❒	❒	❒

Questionnaire completed by:
☐ Patient
☐ Study personnel with patient

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