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DEPARTMENT OF Population Sciences

TITLE: Assessment of the reproducibility and accuracy of a portable system for early detection of cardiac dysfunction in childhood cancer survivors

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Clinical Trial Protocol

Assessment of the reproducibility and accuracy of a portable system for early detection of cardiac dysfunction in childhood cancer survivors

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PROTOCOL SYNOPSIS

Protocol Title

Assessment of the reproducibility and accuracy of a portable system for early detection of cardiac dysfunction in childhood cancer survivors

Study Detail

Population/Indication(s):	Childhood Cancer Survivors (Cancer diagnosis prior to 22 years of age)
Phase:	N/A
Sample Size:	200
Estimated Accrual Duration:	1 Year
Estimated Study Duration	2 Years
Participant Duration:	Approximately 1 week

Study Design

This is a cross-sectional evaluation of 200 childhood cancer survivors who previously underwent a one-time assessment of cardiac function by echocardiogram (echo) and Cardiac Magnetic Resonance (CMR) Imaging between November 2014 and May 2017 (IRB# 14154). We plan to evaluate the reliability and cost-effectiveness carotid pulse-wave based measurement of cardiac ejection fraction using tonometry-based systems in clinical (SphygmoCor® Xcel) and home based (Oscar 2™) settings.

Objectives

Primary Objective(s)

- Validate the accuracy of ejection fraction, as measured using a tonometry-based system (SphygmoCor® Xcel), in the clinic setting, and determine the reproducibility (Oscar 2™) at home.

Secondary Objective(s)

- Determine the cost-effectiveness of tonometry-based screening in the clinic setting and at home.

Methods Description

Study participants will undergo repeat measurement of ejection fraction by echo, CMR and a one-time measurement of carotid pulse wave in the clinical setting (SphygmoCor® Xcel) and will be taught how to obtain BP measurements by the portable Oscar 2™ device in the home setting. Participants will be asked to perform their home-based measurements within 1-5 days of the clinical assessment, allowing us to directly compare measurements obtained by survivors to those by research personnel.

Main Eligibility Criteria

Main Inclusion Criteria

- Previously enrolled in IRB# 14154.

Main Exclusion Criteria

- Participants cannot be actively receiving cancer-directed therapy.
- Standard exclusion for CMR will be incorperated, and these include implated pacemaker or defibrillator, insulin pump, cochlear implant, central nervous system aneurism clips, implanted neural stimulator, occular foreign body (metal), other implanted medical devices (e.g. drug infusion ports).

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ABBREVIATIONS

Abbreviation	Meaning
2D	Two-dimensional
AE	Adverse Event
BLE	Bluetooth Low Energy
BP	Blood Pressure
CFR	Code of Federal Regulations
COH	City of Hope
CMR	Cardiac Magnetic Resonance
CMS	Centers for Medicare & Medicaid Services
CTCAE	Common Terminology Criteria for Adverse Events
DSMC	Data & Safety Monitoring Committee
DSMP	Data & Safety Monitoring Plan
Echo	Echocardiography
EKG	Electrocardiogram
EF	Ejection Fraction
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
IRB	Institutional Review Board
LoA	Limits of Agreement
LV	Left Ventricular
mHealth	Mobile Health
NCI	National Cancer Institute
NIH	National Institutes of Health
PCP	Primary Care Provider
PHI	Protected Health Information
PI	Principal Investigator
SAE	Serious Adverse Event
SD	Standard Deviation
UP	Unanticipated Problem
ABPM	Ambulatory Blood Pressure Monitor
PWV	Pulse Wave Velocity

1.0 OBJECTIVES

1.1 Primary Objective

- Validate the accuracy of ejection fraction, as measured using a tonometry-based system (SphygmoCor® Xcel), in the clinic setting, and determine the reproducibility (Oscar 2™) at home.

1.2 Secondary Objective

- Determine the cost-effectiveness of tonometry-based screening in the clinic setting and at home.

2.0 BACKGROUND

2.1 Disease Indication and Unmet Need

2.1.1 Risk of Congestive Heart Failure in Childhood Cancer Survivors

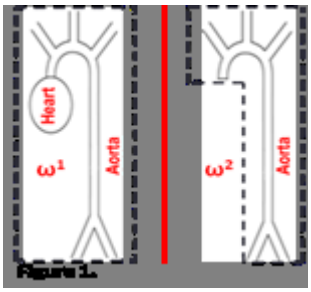
Anthracyclines are among the most effective antineoplastic therapies and are used in nearly 60% of childhood cancer patients. One of the most widely-recognized side-effects of anthracyclines is dose-dependent heart failure that usually develops years after completion of cancer treatment.[1] Overall, childhood cancer survivors are at a 4-fold increased risk of heart failure when compared to age-matched sibling controls,[2,3] and it is estimated that 1 in 10 children treated with high-dose (≥250 mg/m²) anthracyclines will eventually develop heart failure.[4] Improvements in treatment and supportive care have resulted in a rapid increase in the number of childhood cancer survivors. These survivors are expected to constitute a significant proportion of the US population at risk for preventable heart disease in adult life.[5,6]

2.1.2 Natural History of Cardiotoxicity

Anthracycline cardiotoxicity is thought to be related to a combination of free-radical and topoisomerase IIB-mediated direct myocardial injury.[7] If enough myocardial injury occurs, the heart expands in size and the chamber walls become thinner, creating a clinical picture similar to dilated cardiomyopathy.[8] The characteristically delayed manifestation of heart failure after anthracycline exposure is likely related to the eventual failure of a reduced number of unhealthy cardiomyocytes in response to the increase in myocardial wall stress.[9,10] Importantly, it is well-recognized that there is a variable period of asymptomatic cardiac dysfunction that precedes symptomatic disease, which offers a window for early detection and improved management of cardiac dysfunction.[9] Asymptomatic cardiac dysfunction can be identified as abnormalities of cardiac function on imaging studies (e.g. abnormal left ventricular [LV] ejection fraction), allowing for initiation of pharmacologic therapy to delay or prevent the onset of symptomatic heart failure. Echo is the most widely available platform to assess EF, and current survivorship guidelines recommend lifelong echo-based screening for all anthracycline-exposed survivors. However, survivorship care providers and researchers have increasingly questioned the role of echo for population-based screening due to the wide inter- and intra-observer variability of echo-based EF.[11] More accurate platforms such as cardiac magnetic resonance (CMR) imaging can overcome the limitations of echo, but the use of CMR is limited due to its significant cost and lack of wide availability. Thus, there is an urgent need to identify accurate as well as accessible screening strategies for at-risk survivors.

2.1.3 Novel accessible and accurate strategies for cardiac function assessment

A research team at California Institute of Technology (Co-I M. Gharib) recently developed a novel algortihm that utilizes a systems-based approach to evaluate cardiac function by using the measurements obtained from the carotid pulsewave. In brief, the platform relies on the concept that LV and arterial vasculature act as a coupled hemodynamic system before the aortic valve closes, expressed as a dominant frequency (ω_1); **Figure 1**.[12,13] After valve closure, they become decoupled from one another, and the resultant frequency (ω_2) reflects the dynamics inside the aorta and its branches.[12,13] Using non-invasive data capture, we are able to extract metrics that correlate with a person's cardiac function via analysis of hemodynamic waveforms using cardiovascular intrinsic frequency.[13,14] This strategy has been successfully utilized in non-oncology populations, but has not been prospectively validated in a prospective cohort setting.



2.1.4 The high cost of cardiac screening

Our investigative team (S. Armenian, F.L. Wong) recently evaluated the cost-effectiveness of the current cardiac screening guidelines for childhood cancer survivors.[15] We found that although routine cardiac screening is cost-effective, the cost of screening by echo is the greatest contributor to lifetime screening cost (>$55,000 per person)[15]—the lifetime cost for the estimated 300,000 childhood cancer survivors in the US exposed to anthracyclines is thus expected to exceed $16 billion.[16] As such, it is imperative that accurate yet inexpensive alternatives be pursued for monitoring these patients. Concerns regarding the rising lifetime cost of echo-based screening are also relevant for the growing number of adult-onset cancer survivors (e.g. hematologic malignancy, breast cancer) treated with cardiotoxic therapies—the combined healthcare costs for this group of patients are expected to exceed $50 billion in the year 2020 alone.[17]

2.1.5 Urgent need for remote delivery of survivorship care

It is well-recognized that when childhood cancer survivors transition from the cancer center to the primary care setting, they no longer see their oncology team on a regular basis, and rarely visit survivorship care specialists.[18] Thus, the long-term preventive care of these survivors is scattered across hundreds of thousands of individual primary care providers (PCPs). Although these survivors do seek primary care—more than 90% have seen their PCPs in the past two years—it is not in the cancer center context, where knowledge about the link between cancer-specific risk factors (e.g. anthracyclines) and heart disease is known.[19] As a result, <30% of long-term childhood cancer survivors report having undergone risk-based cardiac screening.[19] Survivors living in rural communities are especially affected by the disparities in access to specialized survivorship centers. Tonometry-based screening has the potential to bridge the gap in optimal delivery of risk-based survivorship care by allowing point-of-care cardiac assessment by PCPs in the community, or by facilitating home-based surveillance by specialized survivorship centers.

2.2 About the Current Study

This study is a cross-sectional evaluation of 200 childhood cancer survivors who previously underwent a one-time assessment of cardiac function by echo, CMR, and a tonometry-based system between November 2014 and May 2017 (IRB# 14154). Study participants will undergo repeat measurement of EF by echo and CMR and will have their carotid pulsewave measured by tonometry using SphygmoCor® Xcel in the clinical setting. The pulsewave measurements obtained from the SphygmoCor® Xcel will then be utilized to derive the participant EF. Participants will also be taught how to obtain pulsewave measurements by the portable version of the SphygmoCor® Xcel, which is the Oscar 2™, allowing them to use it in the home setting. Participants will be asked to perform their home-based measurements within 1-5 days of the clinical assessment, allowing us to directly compare measurements obtained by survivors to those by research personnel.

2.3 Study Rationale

This study focuses on an emerging and critically important clinical finding—the greatly increased risk of heart failure in childhood cancer survivors, with its associated high burden of morbidity—and includes several innovative approaches to address this serious threat to survivors' health and quality of life, as outlined below.

- Our proposal builds on well-established evidence that early screening for cardiac dysfunction is effective and introduces a new approach to easily integrate cardiac screening in the community setting.
- We are using a very cost-efficient and scalable approach that will provide healthcare providers with real-time access to vital information regarding change in cardiac function in vulnerable cancer survivors.

• We are responding to the demands of a relatively young population (70% are <40 years of age) of childhood cancer survivors who are technology-engaged and willing to consider remote mobile health (mHealth)-promotion programs to maintain their well-being.

Completion of the proposed research will be a major step toward building an integrative mHealth platform that will allow real-time screening and management of the most common health conditions (e.g. cardiac dysfunction, hypertension, diabetes, overweight/obesity) in childhood cancer survivors. The growing population of childhood cancer survivors (>500,000 alive in the U.S. today) makes development of such strategy's imperative, to ensure that these survivors live long and healthy lives well after their cancer treatment.

3.0 ELIGIBILITY CRITERIA

Participants must meet all of the following criteria on screening examination to be eligible to participate in the study:

3.1 Inclusion Criteria

1. Previously enrolled in IRB# 14154.
2. Able to understand and sign the study specific Informed Consent Form (ICF).

3.2 Exclusion Criteria

1. Participants cannot be actively receiving cancer-directed therapy.
2. Standard exclusion criteria for CMR imaging will be incorporated, and these include: implanted pacemaker or defibrillator, insulin pump, cochlear implant, central nervous system aneurismal clips, implanted neural stimulator, ocular foreign body (metal), other implanted medical devices (e.g.: drug infusion ports).

4.0 PARTICIPANT ENROLLMENT

4.1 Screening and Recruitment

We will identify eligible individuals from an existing electronic database of long-term childhood cancer survivors who previously participated in IRB# 14154. A member of the study team will pre-screen all patients that were previously enrolled in IRB# 14154 by reviewing the medical charts and will exclude anyone with conditions or reasons that may prohibit study entry. All eligible participants will be sent a letter (mail, email, or MyChart) briefly introducing the study, with instructions detailing how to contact research personnel if they have any questions. A member of the study team will follow up on the letter to gauge the survivor's interest.

4.2 Informed Consent Process

Informed consent will be obtained in person or via mail, electronic mail, or by DocuSign™ to obtain electronic signatures from each patient per standard practice. At the time of consent, the study will be reviewed with the subject either by a study investigator or clinician or by a specially trained clinical research personnel member who will answer any questions that the subject may have prior to signing consent. Informed consent will be obtained from each subject who agrees to participate. The investigational nature and objectives of the study, the procedures involved, and their possible risks and discomforts will be carefully explained while obtaining informed consent. Subjects that agree to participate will be given a signed copy of the consent form and experimental subjects' bill of rights to keep. The Principal Investigator will be available to speak to the subject in the event that the subject asks

a question that the consenter is unable to answer or if the subject requests to speak with the Principal Investigator.

5.0 METHODS

5.1 Study Overview

Participants will be scheduled to come to City of Hope for a one-time assessment of cardiac function by echo, CMR, and the SphygmoCor® Xcel system. On the day of the SphygmoCor® Xcel -based measurement, a member of the study team will also train the participant on how to use the Oscar 2™ ABPM system. The participant will be asked to demonstrate that they can take accurate measurements. Once he/she can obtain three accurate readings, they will be sent home with an Oscar 2™ ABPM to perform measurements in a home-based setting. The Oscar 2™ ABPM platform only records the Subject ID assigned to each participant and PI's last name in addition to the measurements collected by the BP monitor and so no identifying information is captured nor stored by Oscar 2™ ABPM.

5.2 Study Procedures

5.2.1 Echocardiographic Evaluation

We will assess cardiac function and mechanics using comprehensive 2D echocardiography with Doppler imaging. Cardiac structure and function will be quantified at rest as recommended by the American Society of Echocardiography and the European Association of Cardiovascular Imaging practice guidelines.[20] We will record heart rate, quantify LV volumes in systole and diastole in the apical 4- and 2-chamber views in triplicate using the biplane method of discs to calculate EF, as recommended by the ASE.[21] At rest, we will estimate SV using the equation: SV = (LV outflow tract diameter/2)^2 × LV outflow tract velocity time integral (VTI). We will also derive effective arterial elastance (E_a), end-systolic elastance (E_{es}), and E_a/E_{es}. E_a, which is a measure of systemic arterial stiffness, will be estimated as end-systolic pressure (ESP)/SV, and ESP will be estimated as 0.90 x systolic pressure, obtained by blood pressure (BP) cuff at the time of the echo. E_{es} is a measure of LV contractility, and will be derived using a modified single-beat algorithm using BP, SV, pre-ejection and total systolic ejection timing intervals.[22] VA coupling provides insight into chamber efficiency and is also predictive of cardiac dysfunction and will be indexed by the ratio E_a/E_{es}. We will also obtain detailed measures of *LV diastolic function*, including pulsed Doppler measurement of mitral valve inflow, peak velocities of early filling (E-wave) and filling during atrial systole (A-wave), mitral annular myocardial e' and a' velocities, mitral E/A and E/e' ratios, and mitral deceleration time. We will evaluate *peak systolic strain* using commercially available analysis software (EchoPAC vBT08; GE Healthcare, USA). Measurements will include peak longitudinal (global and all LV segments), as well as regional and global circumferential strain.[23]

A de-identified copy of the digitized images will be sent to the cardiology lab where LV dimensions, volumes, and EF will be measured by a single cardiologist (Co-I F. Jamal) who will be blinded to clinical and treatment history of participants.

5.2.2 CMR Imaging

CMR imaging will be performed on the same day using a commercially available Vida 3T scanner (Siemens Healthineers USA) equipped with parallel imaging methods, electrocardiographic gating, and an 8-channel cardiac phased-array coil. LV volumes and EF will be obtained using breath-hold ECG-gated 2D cine steady-state free-precession sequences in the 2-, 3-, 4-chamber, and contiguous short-axis orientations. Computation of end-systolic and end-diastolic volumes will be performed by trained research personnel—we have demonstrated excellent intra- and inter-observer (research personnel: study cardiologist) correlations for LV volume measurements (correlation coefficient range 0.91–0.99) in previous studies.

As in echocardiograms, a de-identified copy of the digitized images will be sent to the CMR lab where LV dimensions, volumes, and EF will be measured by a single cardiologist (Co-I H. Narayan) who will be blinded to clinical and treatment history of participants.

5.2.3 SphygmoCor® Xcel and Oscar 2™ ABPM -based Capture of Cardiac Function

Description: The SphygmoCor® Xcel and Oscar 2™ ABPM devices use a standard brachial cuff to measure brachial systolic and diastolic pressures as well as tonometry while capturing brachial waveform. Additionally, the device uses a thigh cuff to capture aortic pulse wave velocity (PWV) measurements using the aid of a carotid tonometer. During the visit, the Xcel device will first be used with a BP cuff to obtain routine blood pressure measurements of systolic and diastolic pressure before the cuff partially re-inflates to capture the brachial waveform. Afterwards, the study staff will switch to thigh cuff and carotid tonometer to capture blood pressure waveforms at the carotid and femoral sites. These data points are then analyzed by the SphygmoCor® Xcel software, deriving ascending aortic waveform and PWV using a validated mathematical transfer function, and displaying the calculated data alongside other noninvasive central blood pressure measurements recorded. SphygmoCor® Xcel and Oscar 2™ ABPM system has 510(k) U.S. FDA clearance as a medical device to perform non-invasive cardiovascular measurements as an adjunct to manage various cardiovascular conditions.

On the day of examination: Research personnel will place the SphygmoCor® Xcel cuff over the participant's maximum brachial pulse, after palpation of the course of the brachial artery. Afterwards, the research personnel will switch to thigh cuff and carotid tonometer to capture blood pressure waveforms at the carotid and femoral sites. The procedure of collecting the brachial pulse will then be redone using the Oscar 2™ ABPM and cuff. Research personnel will instruct the participant on how to properly put on the cuff and take accurate measurements. The participant will be allowed to demonstrate understanding by taking measurements on themselves until 3 successful measurements are performed. The time of application is defined as the time needed to collect 20-30 good quality arterial waveforms, not to exceed BP cuff inflation time of <180 seconds at one time. Measurements will be obtained from the left (preferred) or right brachial arteries. The SphygmoCor® Xcel and Oscar 2™ ABPM data capture procedures are non-invasive. Measurements made from both systems will be relayed via wired connection to the study laptop that is disconnected from all networks. Recordings will ideally be performed on the same day as the echo and CMR, and research personnel will be blinded to both the echo and CMR results. After the waveforms are collected, cardiac cycles will be selected by a researcher blinded to study participant clinical history, echo, and CMR data. We will use the selected cycles to calculate EF via a specialized algorithm called the Intrinsic Frequency.[13,24,25] In brief, the intrinsic frequency algorithm computes the two dominant dynamic frequencies present within a cardiac cycle before and after the closure of the aortic valve (see A.3, Figure 1). Due to the high nonlinearity of the dynamics of both the LV and arterial systems, we will apply a linear regression model to calculate EF. [13,24,25] Our research team recently automated real-time measurement of EF from these waveforms using artificial-intelligence machine-learning algorithms,[13,24,25] and we will use this approach in addition to previously employed retrospective linear regression techniques.

Instruction for home-based measurement: Study personnel will guide participants on proper anatomic placement of the Oscar 2™ ABPM cuff. To demonstrate competency, participants will be asked to obtain at least three correct measurements in the clinic. In addition, they will be given an instructional brochure that details the proper self-measurement technique. Participants will be asked to take the Oscar 2™ ABPM and associated cuff home with them and perform measurements that day over the interval of 4 hours. The data from at home measurements will be imported into the secure study laptop after the Oscar 2™ ABPM and cuff are returned to research personnel. Research personnel will be available to troubleshoot technical difficulties. Once the participants complete the measurements, they will return the devices back to City of Hope using a pre-paid shipping label and box given to them at their clinic visit. A

member of the research personnel will follow-up to confirm the measurements were completed and the devices were returned.

Receiving, Storage, System Use and Return: Research personnel are responsible for the shipment, receipt, storing, charging, and testing the Oscar 2™ ABPM device. The Oscar 2™ ABPM device components will be cleaned using 70% alcohol wipe upon receipt.

5.2.4 Other Study Procedures

5.2.4.1 Measurement of Blood Pressure, Heart Rate, Body Weight and Height

Blood pressure, heart rate, body height and weight will be measured the day of the clinic visit. Sitting/supine blood pressure and heart rate should be measured after the subject has been sitting quietly for at least 5 minutes. Body height and weight should be measured without shoes, using the same equipment for each study participant whenever possible.

5.2.4.2 Questionnaires

Self-reported and CRA/CRN administered questionnaires will be used to obtain baseline data on demographics, family history, and other CV risk factors.

1. Demographics, and CV risk factors information (Demographics and Cardiovascular Risk Factors Form)
2. Family history (COH DPS Family History Form)

The salient domains captured by these questionnaires include date of birth, gender, race/ethnicity, socioeconomic status, and both familial and environmental CV risk factor.

5.3 Duration of Study Participation

The clinic portion of the study will take approximately 4 to 6 hours, while the home-based measurement, including the return of the Oscar 2™ ABPM, is expected to take no more than 1 week.

6.0 STUDY CALENDAR

All assessments may increase in frequency as clinically indicated.

	Screening	Clinic Visit	At Home
	Remote or City of Hope	At City of Hope	At Participant's Home
Screening	X		
Consent	X		
Vital Signs (Blood Pressure. Heart Rate, Height, Weight)		X	
Echo		X	
CMR		X	
Oscar 2™ ABPM Training		X	
Oscar 2™ ABPM Device Measurements		X	X
Return Oscar 2™ ABPM Device			X#
Questionnaires@		X	

A prepaid return shipping label and box will be given to the participant for shipment back to City of Hope.

@Questionniares will be completed electronically or at the clinic visit.

7.0 HUMAN SUBJECTS ISSUES

7.1 Potential Benefits

Subjects will not receive any additional benefit from participating in the current protocol. The knowledge gained from the current study may be used to develop more comprehensive screening strategies in at-risk populations.

7.2 Potential Risks

The eligibility criteria for the current study have been established to exclude individuals for whom this study is not appropriate. The risks of this study are minor. Some of the questions in the questionnaires may make the participant uncomfortable or anxious. The questionnaires that are being used for this research study have been used before in previous studies. To the best of our knowledge they have not caused anyone serious problems. Furthermore, participants may skip any questions they are not comfortable answering.

Additional protection against risk: In order to protect patients from any potential risks associated with the current study, the following assurances will be adhered to: (1) participation is voluntary and consent to participate can be withdrawn at any point within the study without penalty, (2) prospective patients who do not wish to volunteer for the current study will not lose their access to medical services at the City of Hope, (3) all patients will be informed of foreseeable benefits and risks, (4) all data collected from patients or via medical chart review will be stored in a secure computer network folder and/or locked file cabinet(s). In addition, patients will be informed that they have the right to refuse to continue their participation without penalty if they experience significant emotional discomfort, or for any other personal reason. If significant distress is evident during the study, patients will be encouraged to seek appropriate treatment, and a list of referrals will be provided as needed.

8.0 STATISTICAL CONSIDERATIONS

8.1 Sample Size, Accrual Rate and Study Duration

- **Total accrual**: We will accrue up to 200 participants (180 evaluable participants - we estimate 10% of participants will have inevaluable cardiac measurements due to technical difficulty). Accrual is expected to be completed in 1 year.
- **Study duration** is expected to be about 2 years (1-year complete accrual + 1 year for data analysis and manuscript preparation).
- **Participant duration** will be about 1 week.

8.2 Statistical Analysis Plan

We will generate descriptive statistics for participants' demographics, lifestyle behaviors (physical activity, tobacco use), family history of CVD, history of cardiovascular risk factors and other comorbidities (e.g. hypertension, diabetes, dyslipidemia, thyroid disease), including relevant cancer and non-cancer CVD Risk Scores, and cancer treatment-related exposures. We will assess participation bias by comparing demographics (age, gender, race/ethnicity) and treatment-related exposures among participants and non-participants. We will use a two-sided Type I error=0.05,

Specific Aim 1: Validate the accuracy of ejection fraction, as measured using a tonometry-based system (SphygmoCor® Xcel), in the clinic setting, and determine the reproducibility (Oscar 2™) at home..

Our *working hypotheses* are that*:* 1.1**)** In-clinic SphygmoCor® Xcel-derived mean EF will be comparable to that obtained using CMR, but lower than that obtained using echo; and 1.2**)** Home-based, self-measured Oscar 2™ ABPM EF will be comparable to Oscar 2™ ABPM EF obtained by research personnel.

Analytic plan for clinic-based assessment: We will compare EF across the three diagnostic platforms and will generate Bland–Altman plots to evaluate agreement between echo and CMR, SphygmoCor® Xcel and CMR, and echo and the SphygmoCor® Xcel system. The distribution of the difference between two screening approaches will be checked for normality, and 1-sample t-test will be used to test if the mean difference (D) varies from 0. Limits of agreement (LoA) will be computed as the usual 95% upper and lower confidence limits based on D and its standard deviation (SD). The lower and upper confidence limits of LoA will be calculated and compared against the maximum allowable limits to determine if the approaches are in agreement or not. Maximum allowable limits for SphygmoCor® Xcel vs. CMR, echo vs. CMR, and SphygmoCor® Xcel vs. echo will be 5%,10%, 20%. Regression analysis will be performed to examine proportional bias by the magnitude of the mean measured EF. We will calculate Pearson correlation coefficients between EF obtained from echo, CMR, and SphygmoCor® Xcel. We will also compare previously obtained (IRB# 14154) tonometry-based EF to that from the current study, allowing us to describe correlations and change over time. Sensitivity, specificity, false-negative rate, and false-positive rates will be calculated to assess the accuracy of SphygmoCor® Xcel as well as echo for detection of abnormal EF compared to CMR (gold standard). The selected cutoff for abnormal (EF <45%) will be per established thresholds in oncology (refs) and non-oncology populations (refs), as it is a clear indicator for referral to a cardiologist for clinical assessment. We will perform similar analyses to explore the accuracy of SphygmoCor® Xcelfor detecting cardiac dysfunction at higher EF thresholds (e.g. <50%, <55%), given the emerging data on the prognostic value of less pronounced (EF 46%–54%) abnormalities in childhood cancer survivors. *Analytic plan for home-based assessment:* We will generate Bland–Altman plots to evaluate agreement between clinic-(SphygmoCor® Xcel) and home-based (Oscar 2™ ABPM) measurements; 1-sample t-test will be performed to examine whether the mean difference between the two approaches differs from 0. LoA and the upper and lower confidence limits of LoA will be computed, with the latter limits compared to x as the maximum allowable limits. Linear regression analysis will be performed to examine for proportional bias by the magnitude of EF.

Power calculations: We conservatively estimate that of the 221 participants enrolled on IRB# 14154, 200 will agree to participate in the current study. Based on our previous experience, we anticipate that a minimum of 180 out of 200 study participants (90% of the cohort) will have a measurable EF from all (echo, CMR, SphygmoCor® Xcel) modalities. In Bland–Altman analysis, measurements from two methods will be considered in agreement if the confidence intervals of the LoA are within the maximum allowable difference. LoA and its confidence intervals depend on D and SD of the pair of approaches compared. Based on our prior study, we assumed D and SD to be 0.24 and 7.7 for tonometry-based vs. CMR, 4.93 and 10.9 for Echo vs. CMR, and 5.19 and 13.0 for tonometry-based vs. Echo comparisons. Given a confidence level of the LoA of 0.95, 180 participants will provide 80% power to detect agreement when the maximum allowable difference for SphygmoCor® Xcel vs. CMR comparison is 18.4, Echo vs. CMR is 30.2, and SphygmoCor® Xcel vs. Echo is 35.4. Anticipating challenges of implementing home-based measurement of EF, we estimate there will be a minimum of 170 study participants (85% of the cohort) who will have both clinic- and home-based EF available for review. The confidence level of the LoA and its confidence intervals are assumed to be 0.95. For D ranging from 0 to 5 and SD from 5 to 7.7, 170 participants will provide 80% power to detect agreement when the maximum allowable mean difference between clinic- and home-based EF measurement ranges from 12.0 to 23.0.

Specific Aim 2 Determine the cost-effectiveness of tonometry-based screening in the clinic setting and at home.

Our *working hypothesis* is that home-based (Oscar 2™ ABPM) screening will be a cost-effective alternative to in-clinic echo or CMR-based screening.

Analytic plan: The outcome of interest will be cardiac dysfunction detected by each screening modality applied at a single screening session. A Markov model will be used to compare screening approaches, with varying probabilities of asymptomatic cardiac dysfunction according to clinical covariables (e.g. age, sex, anthracycline dose) for each screening approach. We will apply the sensitivity and specificity of echo, CMR, and the Oscar 2™ ABPM system (clinic, home-based) to compare the number of asymptomatic cardiac dysfunction cases identified via each method. Screening costs for echo and CMR, including costs of clinical services, will be obtained from the 2020 Centers for Medicare & Medicaid Services (CMS). We will assume a range of costs for the Oscar 2™ ABPM system ($1,000-1,500) and will estimate attendant clinical services from the CMS. We will compute the cost per cardiac dysfunction diagnosed by each modality. In addition, we will compute the cost per additional cardiac dysfunction identified by a screening device relative to a comparator (e.g. Oscar 2™ ABPM vs. CMR). If the cost per additional cases diagnosed is less than a willingness-to-pay threshold (e.g.$100,000), the screening approach will be deemed cost-effective relative to the comparator. Although some study participants will not be Medicare beneficiaries, Medicare's reimbursement methodology was developed to reflect true resource costs. This methodology has been employed in economic analyses of other cancer screening interventions. We will use sensitivity analysis to assess the impact of assumptions and uncertainty on results and conclusions.

9.0 DATA HANDLING, DATA MANAGEMENT, RECORD KEEPING

9.1 Source Documents

Source documents are original documents, data, and records (e.g., medical records, questionnaires) that are relevant to the research study. The Investigator or their designee will prepare and maintain adequate and accurate source documents. These documents are designed to record all observations and other pertinent data for each patient enrolled in this research study. Source documents must be adequate to reconstruct all data transcribed into data entry forms.

9.2 Data Capture Methods and Management

Data for this study will be collected using REDCap, a secure web application for building and managing online surveys and databases, that is compliant with 21 CFR Part 11. A member of the study team will enter data pertaining to the participant's visits into REDCap.

9.3 Data Entry

The Investigator is responsible for all information collected on subjects enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator. All data entry must be completed by designated study personnel.

9.4 Regulatory Records

The Investigator will maintain regulatory records, including updating records in accordance with Good Clinical Practice guidelines and FDA regulations.

10.0 REPORTING OF ADVERSE EVENTS, UNANTICIPATED PROBLEMS & OTHER EVENTS OF INTEREST

The research team is responsible for classifying adverse events (AEs) and unanticipated problems (UPs) as defined in the relevant regulations and reporting to all applicable parties, including but not limited to the COH IRB, DSMC, Food and Drug Administration (FDA), National Institutes of Health (NIH) and other collaborators, e.g., pharmaceutical companies. The research team is responsible for the continued monitoring and tracking of all AEs in order to ensure non-reportable events are reviewed and monitored and do not rise to a reporting level.

10.1 Assessment of Adverse Events

The site Investigator will be responsible for determining the event name, and assessing the severity (i.e., grade), expectedness, and attribution of all adverse events as applicable per the City of Hope Clinical Research Adverse Event and Unanticipated Problem policy, Adverse events will be characterized using the descriptions and grading scales found in NCI CTCAE v5.0. A copy of the scale can be found at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm.

The following definitions will be used to determine the causality (attribution) of the event to the study agent or study procedure.

- **Unrelated –** The event is clearly NOT related to study treatment and is clearly related to other factors such as the participant's clinical state, other therapeutic interventions, or concomitant medications administered to the participant.
- **Unlikely –** The event is unlikely related to the study treatment and is most likely related to other factors such as the participant's clinical state, other therapeutic interventions, or concomitant drugs.
- **Possible –** The event may be related to study treatment, as it follows a reasonable temporal sequence from the time of drug administration but could have been produced by other factors such as the participant's clinical state, other therapeutic interventions, or concomitant drugs.
- **Probable –** The event is most likely related to the study treatment, as it follows a reasonable temporal sequence from the time of drug administration and a known response pattern to the study drug, and is unlikely related to the participant's clinical state, other therapeutic interventions, or concomitant drugs.
- **Definite –** The event is clearly related to the study treatment, as it follows a reasonable temporal sequence from the time of drug administration and a known response pattern to the study drug, and is not reasonably explained by other factors such as the participant's condition, therapeutic interventions, or concomitant drugs.

10.2 Routine AE Collection and Reporting Guidelines

AEs will be collected from the signing of informed consent until ending study participation. AEs will be monitored by members of the study team. AEs reported through expedited processes (e.g., reported to the IRB, DSMC, FDA, etc.) must also be reported in routine study data submissions.

10.3 Expedited Reporting

Serious Adverse Events that require expedited reporting and unanticipated problems will be reported according to the approved City of Hope Clinical Research Adverse Event and Unanticipated Problem policy.

11.0 ADHERENCE TO THE PROTOCOL & REPORTING OF PROTOCOL DEVIATIONS

Deviations from the protocol should be avoided, except when necessary to eliminate immediate hazard(s) for the protection, safety, and well-being of a research participant. As a result of deviations, corrective actions are to be developed by the research personnel and implemented promptly.

11.1 Reporting by COH

All protocol deviations and planned protocol deviations will be reported in accordance with the City of Hope Clinical Research Protocol Deviation policy.

12.0 STUDY OVERSIGHT, QUALITY ASSURANCE, & DATA AND SAFETY MONITORING

12.1 All Investigator Responsibilities

An investigator is responsible for ensuring that a research study is conducted according to the protocol, and applicable regulations; for protecting the rights, safety, and welfare of participants under the investigator's care are followed.

12.2 Study Principal Investigator Responsibilities

The Study Principal Investigator is responsible for the conduct of the research study, including overseeing that responsibilities are executed in accordance with federal regulations.

12.3 Protocol Management Team (PMT)

The Protocol Management Team (PMT), minimally consisting of the study PI, collaborating investigators, clinical research associate/coordinator, and the study biostatistician, is responsible for ongoing monitoring of the data and safety of this study, including implementation of the stopping rules for safety/toxicity.

The PMT is recommended to meet (in person or via teleconference) to review study status. The meeting is a forum to discuss study related issues including accrual, SAE/AE/UPs experienced, study response, deviations/violations, and study management issues. The appropriateness of further participant enrollment and the specific intervention for subsequent participant enrollment are addressed.

12.4 Quality Assurance

Clinical site auditing is conducted to ensure that the rights of human subjects are protected, that the study is implemented in accordance with the protocol and regulatory requirements, and that the quality and integrity of study data and data collection methods are maintained. This research study will be audited by the City of Hope Office for Safety and Data Quality. Details of clinical site auditing are documented in the City of Hope Institutional Data and Safety Monitoring Plan (DSMP).

12.5 Risk Determination

This is a low risk study, as defined in the City of Hope Institutional Data and Safety Monitoring Plan (DSMP), because it is a non-interventional study using non-invasive testing and therefore the risk of harm is low. The SphygmoCor® Xcel system SphygmoCor® Xcel system and Oscar 2™ ABPM do not meet the definition for a significant risk device in accordance with 21 CFR 812.2(b) (1) (ii). NSR device studies do not have to have an IDE application approved by FDA. The study Principal Investigator is responsible for monitoring protocol conduct and reporting all reportable events to the City of Hope (COH) Data and Safety Monitoring Committee (DSMC) and Institutional Review Board (IRB) in accordance with the City of Hope Institutional Deviation policy, and Clinical Research Adverse Event and Unanticipated Problem policy.

12.6 City of Hope Data and Safety Monitoring Committee

The COH Data and Safety Monitoring Committee (DSMC) will review and monitor study progress, compliance, safety, and accrual data from this research study via the PMT Progress Report (submitted by the Study Principal Investigator according to the frequency outlined in the City of Hope Institutional DSMP). The DSMC is composed of clinical specialists who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Protocol Management Team.

13.0 ETHICAL AND REGULATORY CONSIDERATIONS

13.1 Ethical Standard

This study will be conducted in conformance with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research (US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, April 18, 1979) and the Declaration of Helsinki.

13.2 Regulatory Compliance

This study is to be conducted in compliance with the IRB approved protocol and according to the following considerations:

- US Code of Federal Regulations (CFR) governing clinical study conduct
  - Title 21 Part 11 – Electronic Records; Electronic Signatures
  - Title 21 Part 50 – Protection of Human Subjects
  - Title 21 Part 54 – Financial Disclosure by Clinical Investigators
  - Title 21 Part 56 – Institutional Review Boards
  - Title 21 Part 58 – Good Laboratory Practice for Nonclinical Laboratory Studies
  - Title 45 Part 46 – Protection of Human Subjects
- US Federal legislation, including but not limited to
  - Health Insurance Portability and Accountability Act of 1996
  - Section 801 of the Food and Drug Administration Amendments Act
- Applicable state and local laws. For research occurring in California, this includes but is not limited to State of California Health and Safety Code, Title 17
- Applicable NIH policies and procedures
- Applicable institutional research policies and procedures

13.3 Institutional Review Board

An Institutional Review Board (IRB) that complies with the federal regulations at 45 CFR 46 and 21 CFR 50, 56 and State of California Health and Safety code, Title 17, must review and approve this protocol, informed consent form and any additional documents that the IRB may need to fulfill its responsibilities (Investigator's Brochure, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) prior to initiation of the study. Revisions to approved documents will require review and approval by the IRB before the changes are implemented in the study. All institutional, NCI, Federal, and State of California regulations must be fulfilled.

The IRB's written unconditional approval of the study protocol and the informed consent document must be in the possession of the investigator before the study is initiated.

The IRB will be informed of serious unexpected, unanticipated adverse experiences, and unanticipated problems occurring during the study, and any additional adverse experiences in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

13.4 Informed Consent

The Principal Investigator or IRB approved named designee will explain the nature, duration, purpose of the study, potential risks, alternatives and potential benefits, and all other information contained in the informed consent document. In addition, they will review the experimental subject's bill of rights if applicable, and the Health Insurance Portability and Accountability Act (HIPAA) research authorization form. Prospective participants will be informed that they may withdraw from the study at any time and for

any reason without prejudice, including as applicable, their current or future care or employment at City of Hope or any relationship they have with City of Hope. Prospective participants will be afforded sufficient time to consider whether or not to participate in the research.

After the study has been fully explained, written informed consent will be obtained from either the prospective participant or his/her guardian or legal representative before study participation. The method of obtaining and documenting the informed consent and the contents of the consent must comply with the ICH-GCP and all applicable regulatory requirements.

A copy of the signed informed consent will be given to the participant or his/her legally authorized representative. The original signed consent must be maintained by the investigator and available for inspection by regulatory authority at any time.

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation.

13.5 Participant Withdrawal

Participants may withdraw from the study at any time and for any reason without prejudice. The withdrawal must be documented per institutional policies.

Participant withdrawal may consist of any of the following with regard to study procedures and data collection:

- Withdrawal from study treatment, all active procedures, and any future data collection.

13.6 Special and Vulnerable Populations

13.6.1 Women and Minorities and Other Underrepresented Populations

The study is open to anyone regardless of gender, race or ethnicity. Efforts will be made to extend the accrual to a representative population impacted by the disease under study and among populations with the City of Hope catchment area. If differences in outcome that correlate to gender, racial, or ethnic identity are noted, accrual may be expanded or additional studies may be performed to investigate those differences more fully.

13.6.2 Vulnerable Populations

Per 45 CFR §46.111 (a)(3) and 45 CFR §46, Subparts B-D identifies children, prisoners, pregnant women, mentally incapacitated persons, and economically or educationally disadvantaged persons as vulnerable populations.

Economically/educationally disadvantaged persons are not actively targeted for participation, nor are they excluded from participation. This study does not pose additional risks for economically/educationally disadvantaged persons than for the general population.

13.7 Participant Confidentiality

Participant confidentiality is strictly held in trust by the investigators and the research personnel. This confidentiality is extended to cover testing of biological samples in addition to any study information relating to participants.

This research will be conducted in compliance with federal and state requirements relating to protected health information (PHI), including the requirements of the Health Insurance Portability and Accountability Act of 1996. HIPAA regulations require a signed subject authorization informing the subject of the nature of the PHI to be collected, who will have access to that information and why, who will use or disclose that information, and the rights of a research participant to revoke their authorization for use of their PHI. In

the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For participants that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

Release of research results should preserve the privacy of medical information and must be carried out in accordance with Department of Health and Human Services Standards for Privacy of Individually Identifiable Health Information, 45 CFR 164.508. When results of this study are reported in medical journals or at meetings, identification of those taking part will not be disclosed and no identifiers will be used.

Medical records of participants will be securely maintained in the strictest confidence, according to current legal requirements. Data will be entered, analyzed and stored in encrypted, password protected, secure computers that meet all HIPAA requirements. All data capture records, drug accountability records, study reports and communications will identify the patient by initials and the assigned patient number.

The Investigator/Institution will permit direct access to source data and documents by the FDA, and other applicable regulatory authorities. The access may consist of study-related monitoring, including remote monitoring, audits, IRB reviews, and FDA/regulatory authority inspections. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

13.8 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study Sponsor (City of Hope) prior to participation in this study. All City of Hope investigators will follow the City of Hope conflict of interest policy.

13.9 Financial Obligations, Compensation, and Reimbursement of Participants

In the event of physical injury to a participant resulting from research procedures, appropriate medical treatment will be available at City of Hope to the injured participant. There are no plans for City of Hope to provide financial compensation in the event of physical injury to a participant.

13.9.1 Compensation

The research participant will receive $100 gift card at completion of the clinic visit and an additional $100 gift card upon receipt of their devices and tablet at the end of the study.

13.10 Publication/ Data Sharing

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by City of Hope for the purposes of performing the study, will be published or passed on to any third party without the written approval of the City of Hope PI. Any investigator involved with this study is obligated to provide City of Hope with complete test results and all data derived from the study.

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement between City of Hope. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

In accordance with the U.S. Public Law 110-85 (Food and Drug Administration Amendments Act of 2007 or FDAAA), Title VIII, Section 801, this trial will be registered onto ClinicalTrials.gov; it is City of Hope

policy to register the trial prior to enrollment of the first patient. Results will be reported on ClinicalTrials.gov generally within 12 months after the primary completion date unless criteria to delay submission are met per the final rule.

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

14.0 REFERENCES

1. Lipshultz SE, Adams MJ, Colan SD, et al: Long-term cardiovascular toxicity in children, adolescents, and young adults who receive cancer therapy: pathophysiology, course, monitoring, management, prevention, and research directions: a scientific statement from the American Heart Association. Circulation 128:1927-95, 2013

2. Oeffinger KC, Mertens AC, Sklar CA, et al: Chronic health conditions in adult survivors of childhood cancer. N Engl J Med 355:1572-82, 2006

3. Mulrooney DA, Yeazel MW, Kawashima T, et al: Cardiac outcomes in a cohort of adult survivors of childhood and adolescent cancer: retrospective analysis of the Childhood Cancer Survivor Study cohort. BMJ 339:b4606, 2009

4. van Dalen EC, van der Pal HJ, Kok WE, et al: Clinical heart failure in a cohort of children treated with anthracyclines: a long-term follow-up study. Eur J Cancer 42:3191-8, 2006

5. Barry EV, Lipshultz SE, Sallan SE: Anthracycline-induced cardiotoxicity: natural history, risk factors, and prevention., American Society of Clinical Oncology. Chicago, IL, 2008, pp 448

6. Lipshultz SE, Colan SD: Cardiovascular trials in long-term survivors of childhood cancer. J Clin Oncol 22:769-73, 2004

7. Horenstein MS, Vander Heide RS, L'Ecuyer TJ: Molecular basis of anthracycline-induced cardiotoxicity and its prevention. Mol Genet Metab 71:436-44, 2000

8. Adams MJ, Lipshultz SE: Pathophysiology of anthracycline- and radiation-associated cardiomyopathies: implications for screening and prevention. Pediatr Blood Cancer 44:600-6, 2005

9. Lipshultz SE, Alvarez JA, Scully RE: Anthracycline associated cardiotoxicity in survivors of childhood cancer. Heart 94:525-33, 2008

10. Lipshultz SE, Lipsitz SR, Sallan SE, et al: Chronic progressive cardiac dysfunction years after doxorubicin therapy for childhood acute lymphoblastic leukemia. J Clin Oncol 23:2629-36, 2005

11. Monsuez JJ: Detection and prevention of cardiac complications of cancer chemotherapy. Arch Cardiovasc Dis 105:593-604, 2012

12. Pahlevan NM, Gharib M: Aortic wave dynamics and its influence on left ventricular workload. PLoS One 6:e23106, 2011

13. Pahlevan NM: A Systems Approach to Cardiovascular Health and Disease with a Focus on Aortic Wave Dynamics, Doctoral dissertation, California Institute of Technology, 2013

14. Pahlevan NM, Gharib M: A wave dynamics criterion for optimization of mammalian cardiovascular system. J Biomech, 2014

15. Wong FL, Bhatia S, Kurian S, et al: Efficacy and cost-effectiveness of the Children's Oncology Group (COG) Long-term Follow-up (LTFU) Guidelines in reducing risk of congestive heart failure (CHF) in childhood cancer survivors (CCS). Ann Intern Med In Press, 2014

16. Lipshultz SE, Adams MJ, Colan SD, et al: Long-term Cardiovascular Toxicity in Children, Adolescents, and Young Adults Who Receive Cancer Therapy: Pathophysiology, Course, Monitoring, Management, Prevention, and Research Directions: A Scientific Statement From the American Heart Association. Circulation 128:1927-95, 2013

17. Mariotto AB, Yabroff KR, Shao Y, et al: Projections of the cost of cancer care in the United States: 2010-2020. J Natl Cancer Inst 103:117-28, 2011

18. Zabih V, Kahane A, O'Neill NE, et al: Interventions to improve adherence to surveillance guidelines in survivors of childhood cancer: a systematic review. J Cancer Surviv 13:713-729, 2019

19. Yan AP, Chen Y, Henderson TO, et al: Adherence to Surveillance for Second Malignant Neoplasms and Cardiac Dysfunction in Childhood Cancer Survivors: A Childhood Cancer Survivor Study. J Clin Oncol 38:1711-1722, 2020

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

21. Lang RM, Badano LP, Mor-Avi V, et al: Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 16:233-70, 2015

22. Chen CH, Fetics B, Nevo E, et al: Noninvasive single-beat determination of left ventricular end-systolic elastance in humans. J Am Coll Cardiol 38:2028-34, 2001

23. Geyer H, Caracciolo G, Abe H, et al: Assessment of myocardial mechanics using speckle tracking echocardiography: fundamentals and clinical applications. J Am Soc Echocardiogr 23:351-69; quiz 453-5

24. Pahlevan NM, Rinderknecht DG, Tavallali P, et al: Noninvasive iPhone Measurement of Left Ventricular Ejection Fraction Using Intrinsic Frequency Methodology. Crit Care Med 45:1115-1120, 2017

25. Pahlevan NM, Tavallali P, Rinderknecht DG, et al: Intrinsic frequency for a systems approach to haemodynamic waveform analysis with clinical applications. J R Soc Interface 11:20140617, 2014