ReTEECA Trial. Rescue TransEsophageal Echocardiography for In-Hospital Cardiac Arrest.

Asad Ali Usman (✉ Asad.Usman@pennmedicine.upenn.edu)

University of Pennsylvania <https://orcid.org/0000-0002-3874-9741>

Samantha Stein

University of Pennsylvania Hospital: Hospital of the University of Pennsylvania

Audrey Spelde

University of Pennsylvania Hospital: Hospital of the University of Pennsylvania

Felipe Teran-merino

University of Pennsylvania Hospital: Hospital of the University of Pennsylvania

John Augoustides

University of Pennsylvania Hospital: Hospital of the University of Pennsylvania

Stuart Weiss

University of Pennsylvania Hospital: Hospital of the University of Pennsylvania

Justin Clapp

University of Pennsylvania

William Vernick

University of Pennsylvania Hospital: Hospital of the University of Pennsylvania

Benjamin Abella

University of Pennsylvania Hospital: Hospital of the University of Pennsylvania

Jacob Gutsche

University of Pennsylvania Hospital: Hospital of the University of Pennsylvania

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Abstract

This trial is aimed at studying the utility and interventional outcomes of rescue transesophageal echocardiography (RescueTEE) to aid in diagnosis, change in management, and outcomes during CPR by using a point of care RescueTEE protocol in the evaluation of in-hospital cardiac arrest (IHCA). This is an interventional prospective convenience sampled partially blinded phase II clinical trial with primary outcomes of survival to hospital discharge (SHD) with RescueTEE image guided ACLS versus conventional ACLS.

Statement Of Compliance

The trial will be carried out in accordance with International Conference on Harmonization Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 Protocol Summary

1.1 Synopsis

Title:	Rescue TransEsophageal Echocardiography for In-Hospital Cardiac Arrest (ReTEECA) Trial
Study Description:	<p>This is a Phase II, single center, partially blinded, prospective, safety and efficacy pragmatic clinical trial comparing rescue transesophageal image guided ACLS versus conventional ACLS in adult patients with in-hospital cardiac arrest (IHCA). The ReTEECA Trial will use a recently published and validated focused 5-view RescueTEE protocol to evaluate patients with IHCA to obtain diagnostic and therapeutic information to aid in medical decision-making in a rapid fashion for those patients who are experiencing in-hospital arrest.¹ Patients will be resuscitated with one of the following protocols:</p> <p>1) Conventional ACLS with RescueTEE during IHCA. The TEE probe will be brought to the IHCA code call and placed within 10 minutes of cardiac arrest after a secured airway has been obtained. The RescueTEE team led by a physician (RescueTEE MD) and will use a predefined protocol for diagnosis and if needed intervention at the discretion of the treating physician (Code Team MD). If an intervention is performed this will be done at the discretion of the treating physician as a pragmatic and clinically evidenced intervention. The TEE probe will remain indwelling for 30 minutes or until return of spontaneous circulation (ROSC) whichever is earlier.</p> <p>2) Conventional ACLS without RescueTEE during IHCA. Conventional ACLS will be driven by national American Heart Association (AHA) standardized protocols by the treating physician (Code Team MD) and code team members.</p> <p>Management of the patient and ACLS will be driven pragmatically and by the local code team (Code Team MD) and not the RescueTEE team. Advice and diagnostic evidence, as able, from the RescueTEE will be provided by the RescueTEE team (RescueTEE MD). Post ROSC care will be at the discretion of the ICU team (ICU MD). The indications for using a validated published RescueTEE protocol is to study the outcome effects of an intervention that is publicly available and apply this in a real-world clinical scenario as a prospective trial.</p> <p>Based on our preliminary results we hypothesize that routine use of RescueTEE guided ACLS for IHCA will expedite diagnosis, treatment, intervention, and facilitate and identify reversible causes and significantly improve survival to hospital discharge and in turn functional survival compared to standard ACLS.</p>
Objectives:	<p>Primary Objective: The overall primary objective for the ReTEECA trial is to determine if survival to hospital discharge (SHD) is improved with 1) RescueTEE guided ACLS versus 2) conventional ACLS.</p> <p>Secondary Objective: To determine whether and quantify how TEE guided diagnosis and intervention after in-hospital cardiac arrest leads to improved survival. The goal of the study will be to use intra-arrest RescueTEE diagnostic imaging to guide the code leader in clinical management and decision-making and to therefore decrease IHCA mortality rates by timely diagnosis and intervention. Additionally, we will assess if RescueTEE guidance of intra-arrest therapies or interventions can significantly improve survival to hospital discharge (SHD) as well as functionally favorable outcomes at hospital discharge (NHD).</p>
Endpoints:	<p>Primary Study Endpoint: Survival to hospital discharge (SHD)</p> <p>Secondary Study Endpoint: Survival at specific timepoints as well as with functional outcome - 1) end of code, 2) ICU discharge, 3) 30-days post arrest, 4) 3-months post-arrest neurologically intact survival 5) 6 months post arrest neurologically intact survival and 6) neurologically intact hospital discharge (NHD). Neurologically intact survival is defined as modified Rankin's Score (mRS) of 0-3 at the time of assessment.</p> <p>Additional secondary endpoints include, ascertaining whether RescueTEE can provide clinically meaningful diagnoses intra-arrest and if RescueTEE information can be used in the management of in-hospital arrest. Finally, secondary outcomes include the ability of RescueTEE to provide information that leads to therapeutic guidance or intervention for the code leader during intra-arrest situations</p>
Study Population:	<p>The ReTEECA trial uses the Utstein-style ILCOR task force definitions for cardiac arrest. These definitions include what constitutes in-hospital arrest, cardiac arrest, respiratory arrest, duration, etc.² Sample size is N=514 (257 each arm) in-hospital.</p> <p>Inclusion criteria include:</p>

- All patients greater than 18 years of age
- Intubated or permanent tracheostomy in situ
- Patients being actively intubated as part of ACLS
- In-hospital cardiac arrest

Exclusion

- Unsecured airway
- Aspiration
- History of Tracheoesophageal injury
- History of Tracheoesophageal fistula
- Esophagectomy
- Active upper GI bleeding
- Esophageal Varices
- Ongoing hemoptysis
- Technically challenging TEE placement
- Pregnancy

Phase:	Phase II
Description of Sites/Facilities Enrolling Participants:	Hospital of the University of Pennsylvania Large Academic Quaternary Teaching hospital
Description of Study Intervention:	Equipment: Philips CX50 Portable Ultrasound machine and Philips X8-2t Probe When overhead code calls are placed at the Hospital of the University of Pennsylvania (HUP) the CV anesthesiologist (RescueTEE MD) from the cardiothoracic intensive care unit (CTICU) will travel with the TEE probe and portable laptop ultrasound machine to the code location. If the patient meets the inclusion criteria and all exclusion criteria are reviewed and confirmed then the TEE probe will be introduced into the esophagus and stomach in routine fashion and images obtained. The therapeutic window is defined as the time the code is called until the RescueTEE probe is placed. Due to the urgent nature and diminishing return of RescueTEE and known decreased survival as ACLS progresses the therapeutic window is defined as 10 minutes from the start of the code call. See EFIC for therapeutic window definition and rationale and exception from informed consent documentation and plan. A 5-view RescueTEE protocol will be used that has been published and validated previously. Based on the RescueTEE images specific diagnoses will be ruled in or out and therapeutic interventions recommended by the RescueTEE MD. Interventions will be carried out by the treatment MD team in a pragmatic fashion.
Study Duration:	36 months
Participant Duration:	30 minutes for RescueTEE imaging with image guided ACLS Conventional ACLS. Participation includes neurological screening interview using the mRS as follow up. No further invasive testing will be done beyond the initial RescueTEE guided ACLS. After the IHCA if the patient has ROSC, then the following data will be collected: Both Arms: Chart review and screening interview (non-invasive) ICU Discharge follow up 30 day follow up 3 months follow up + mRS 6 months follow up + mRS Hospital discharge follow up

1.2 Schema

1.3 Schedule of Activities (SoA)

Procedures	Code call Therapeutic Window	IHCA (Rescue TEE ACLS or Conventional ACLS)	ICU/Hospitalization	30- Days	3 months	6 Months	Hospital Discharge
Inclusion							
Exclusion	X						
Randomization	X						
LAR (if possible)	X						
Consent for Continued participation		X	X	X	X	X	X
Demographics		X					
RescueTEE (Probe placement and obtain images)		X					
Medical History		X	X				
Vital signs		X	X				
Code Sheet Recording: Medications administered, Airway type, ROSC, duration, labs, etc		X					
Interventions#: ECMO, Cath lab, PERT, CT, Chest tubes, etc		X	X	X	X	X	
Communication to Code Team/ Decision making		X					
Follow up TTE*			X				
Follow up TEE*			X				
Blinded mRS					X	X	
Adverse Events /Significant adverse events		X	X	X	X	X	X
DSMB		X	X	X	X	X	X

Procedures	Code call	IHCA	ICU/Hospitalization	30-Days	3 months	6 Months	Hospital Discharge
	Therapeutic Window	(Rescue TEE ACLS or Conventional ACLS)					
*: If ordered as routine care							
#: If guided by TEE during ICHA							

2 Introduction

2.1 Study Rationale

There are approximately 290,000 in-hospital cardiac arrests (IHCA) each year in the United States.³ Advanced life support (ACLS) and cardiopulmonary resuscitation (CPR) has been developed by the American Heart Association (AHA) to provide care for these patients and save lives. CPR and ACLS algorithms have been developed with out-of-hospital cardiac arrest (OHCA) in mind. Unfortunately, IHCA and OHCA are clinically and diagnostically quite different. Hospitalized patients are becoming increasingly complex and cutting-edge technologies are now available to manage ICHA. The foundations of CPR including early defibrillation and good quality chest compressions remain paramount to IHCA. Additionally, treatment strategies for patients with IHCA should clearly include achievement of adequate coronary perfusion and cerebral perfusion, optimizing CPR hemodynamics, clear diagnosis, and early intervention. One of the newer aspects of IHCA include early deployment of point of care ultrasound (POCUS). Unfortunately, experiencing an IHCA currently does not confer a survival benefit in spite of being surround by continuous monitoring, immediate access to healthcare providers, and several advanced therapy modalities including immediate acute coronary care.³ Quick deployment of image guided ACLS is feasible for the IHCA patient population due to the resources available in-hospital. POCUS during resuscitation has been suggested to identify underlying otherwise occult causes of arrest (e.g. cardiac tamponade, pulmonary embolism, and dissection) and to help with intra-arrest prognostication whenever used to detect spontaneous cardiac movement. The most recent AHA guidelines provide a class IIb, level of evidence C recommendation for the use of ultrasound as an adjunct to standard patient evaluation.⁴ Transthoracic and transesophageal echocardiography (TTE, TEE) are two imaging modalities that can be deployed rapidly for IHCA. Intra-arresting echocardiography offers the significant opportunity to impact survival and public health.

Rescue transesophageal echocardiography (RescueTEE) is an unplanned ultrasound examination performed on an urgent or emergent basis to diagnose causes of unexpected hemodynamic instability or cardiopulmonary arrest. The indication for RescueTEE is generally based on the individual patient's condition rather than a specific surgical or interventional procedure. POCUS is an imaging methodology performed at the bedside, which allows clinicians to rapidly identify life-threatening pathology in patients who are too critically ill to await formal echocardiography or transport to the echo lab. POCUS RescueTEE is a developing area within anesthesiology, critical care and emergency medicine which provides real time information to help guide therapeutic interventions at the bedside. There are several patients that may benefit from TEE imaging, as opposed to transthoracic echocardiography (TTE), due to underlying structural, functional, or ischemic cardiovascular pathology that is more readily seen on TEE. Due to a variety of technical, logistical (machine positioning, proceduralist location) and/or patient related factors including obesity, ongoing cardiopulmonary resuscitation (CPR), open chest, recent sternotomy, and pulmonary edema; TEE is favored over

TTE.⁵ Factors such as the patient's disease process and anticipated diagnostic dilemmas are considered when deciding which patients will benefit from RescueTEE. Compared with conventional ACLS which uses a non-image based, non-diagnosis based, approach for IHCA, the addition of imaging during ACLS can function to provide early diagnosis and guide therapy. Image guided ACLS is expected to significantly improve functional favorable survival to hospital discharge and long-term outcomes.

Patients who are experiencing IHCA require urgent intervention and are facing a life-threatening situation. Unfortunately, these patients will die unless urgent intervention is provided including but not limited to ACLS and direct therapeutic management addressing the cause of arrest. There are approximately 290,000 IHCA per year in the United States. The mean age is 66 years old and the presenting rhythm is pulseless electrical activity in up to 81% of cases. Fifty to sixty percent of IHCA are caused by a cardiac etiology and fifteen to forty percent are caused by a respiratory etiology.³ The key elements of treatment during cardiac arrest include good quality chest compressions, ventilation, early defibrillation, and when applicable attention to reversible causes such as pulmonary embolism, myocardial infarction, or tamponade.

RescueTEE has been proposed as a well-suited imaging modality during IHCA. TEE is favored over TTE during IHCA due to the fact that it does not interfere with chest compressions, standard ACLS, pulse checks, and provides continuous imaging for the duration of the IHCA. Furthermore, it provides direct feedback for hand positioning, return of spontaneous circulation (ROSC), and can be used for therapeutic intervention and guidance. As stated previously, the most recent AHA guidelines provide a class IIb, level of evidence C recommendation for the use of ultrasound as an adjunct to standard patient evaluation during IHCA and the American College of Emergency Physicians endorses the clinical use of TEE during cardiac arrest.⁶

To implement this POC RescueTEE guided ACLS strategy we instituted a pilot program to assess logistics, feasibility and gauge early outcomes at the Hospital of the University of Pennsylvania. A Redcap case record form (CRF) was created. A data entry portal was installed on all echocardiographer's cellphones at the University of Pennsylvania. Feedback was provided during a pilot period in order to create an informed data dictionary for future trials. A standardized 5-view RescueTEE algorithm was used. The TEE probe was transported to the code by technicians and the anesthesiologists performed the examination after a secure airway was obtained. Anesthesiology led airway teams who attend to cardiac code calls in the hospital were well poised to place RescueTEE probes due to logistics, availability, and already in situ airway teams on campus. A total of 45 exams in 12 weeks were analyzed during the trial run up. TEE exams started on average 7 minutes 33 seconds after code call. The therapeutic window was set at 10 minutes. We found 5 AMI, 2 PE, 1 aortic dissection, 11 acute RV dysfunction, 2 pericardial tamponade, and 1 acute valvular pathology. This helped refine the level of accuracy needed for a trial of this size. Accuracy was defined as the ability to rule in, rule out, or do both with RescueTEE. There were 3 lateral wall and 2 anterior wall MI. There was 1 clot in transit and 1 McConnell's sign for PE. The dissection was classified as type A. The valvular pathology was posterior mitral valve endocarditis. These cases also helped define the degree of precision possible by RescueTEE. Images were reread after one week and there was 100% inter and intra-rater concordance which optimized a fixed and organized process for a future trial. Rescue TEE examinations also helped guide intervention including 7 VA ECMO cannulations, changing vasopressor medications, cardioverting 3 patients, and administering fluid and blood in 2 patients. No injuries occurred. After this pilot period a comprehensive case record form (CRF) was finalized for the ReTEECA trial.

Given the poor clinical outcomes of IHCA it is imperative to conduct research in this area. RescueTEE provides an avenue to help diagnose and clinically intervene on pathology during the intra-arrest period. This directly impacts the disease process, the patient, and will likely change ACLS management. There are studies that have been conducted retrospectively and prospectively that highlight the benefits of image guidance during ACLS; however, no randomized

clinical trial documenting the safety and efficacy of RescueTEE has been conducted. Many institutions and hospital systems are now using RescueTEE during ACLS; however, we do not know the impact that this has had directly on survival and complications. Like many areas in medicine, a prospective clinical trial can help elucidate the direct patient benefits in terms of survival. This will offer future researchers a platform to conduct further studies on image guidance during ACLS. A prospective clinical trial is necessary to transform national guidelines and help guide evidence-based practice throughout the country.

ReTEECA Trial Hypothesis

Based on our preliminary results we hypothesize that routine use of RescueTEE guided ACLS for IHCA will expedite diagnosis, treatment, intervention, and facilitate and identify reversible causes and significantly improve survival to hospital discharge and in turn functional survival compared to standard ACLS.

ReTEECA Trial

We propose a Phase II, single center, partially blinded, intention to treat, safety and efficacy clinical trial to assess the results of routine RescueTEE guided ACLS for IHCA compared with standard ACLS. The Hospital of the University of Pennsylvania and the Department of Anesthesiology and Critical Care has the patient population, experience, expertise, and infrastructure to execute the proposed study.

Specific Aims

The goal of the study will be to use intra-arrest RescueTEE diagnostic imaging to guide the code leader in clinical management and decision-making and to therefore decrease IHCA mortality rates. Additionally, we will assess if RescueTEE guidance of intra-arrest therapies or interventions can significantly improve functionally favorable outcomes.

Primary Study Endpoint

Survival to hospital discharge (SHD)

Secondary Study Endpoint: To determine if TEE guided diagnosis and intervention after in-hospital cardiac arrest leads to improved survival to specific timepoints: 1) end of code, 2) ICU discharge, 3) 30-days, and 4) neurologically intact hospital discharge (NHD) (3 months follow up, 6 months follow up). Neurologically intact survival is defined as modified Rankin's Score (mRS) of 0-3.

Additional secondary endpoints include, ascertaining whether RescueTEE can provide clinically meaningful diagnoses intra-arrest and if that information can be used in the management of in-hospital arrest. Finally, secondary outcomes include the ability of RescueTEE to provide information that leads to therapeutic guidance or intervention for the code leader during intra-arrest situations

Significance

If our study results indicate potential safety and efficacy, it will provide the basis for future multicenter clinical trial to assess definitive survival benefit and generalizability to this approach.

2.2 Background

2.2.1 Clinical Baseline

The public health burden of IHCA is enormous with approximately 290,000 patients who experience IHCA and more than 217,000 death each year in the United States. Survival rates vary by location, hospital type, race, age, and hospital complexity. Despite being surrounded by health care providers and being in a hospital setting survival rates remain around 25%.⁷ Historically, the etiologies of cardiac arrest have been dichotomized as cardiac or non-cardiac. Because patients with no obvious cause are generally classified as cardiac, and because discrepancies often exist between clinical and postmortem diagnoses, the causes of cardiac arrest are often uncertain. In general, cardiac causes of IHCA, such as myocardial infarction, arrhythmia, or heart failure, are most frequent, with a prevalence of approximately 50–60% of all IHCA. Respiratory insufficiency is the second most common cause of IHCA (15%-40%). The median admission duration prior to IHCA is 1 to 2 days, with a higher prevalence of respiratory insufficiency as the cause of cardiac arrest for those with longer duration of preceding hospitalization. Neurological causes of cardiac arrest are rare in the in-hospital setting.⁸

Identifying the cause of IHCA is essential in the management of the patient. During cardiac arrest, guidelines emphasize rapid identification of reversible causes, which are categorized colloquially as the “H’s and T’s”.⁹ Although not all of these categories are applicable for IHCA, the majority of IHCA can be categorized using this approach.¹⁰ Identifying the cause of cardiac arrest should improve outcomes because diagnosis prior to treatment of a disease process is a fundamental clinical corner stone in medicine.⁸ Identification of the cause of cardiac arrest also has implications if ROSC is achieved, because post–cardiac arrest organ dysfunction is partly dependent on the underlying cause, and post–cardiac arrest treatment should be tailored accordingly.

Chest compressions, ventilation, and early defibrillation, as described above are important to achieve ROSC.¹¹ Early initiation of CPR is associated with improved outcomes. CPR training for all hospital personnel is mandatory, facilitating the rapid identification and management of cardiac arrest prior to the arrival of the cardiac arrest team, however this does not include image guidance currently. Quality of chest compressions and CPR in general have been associated with better outcomes in patients with cardiac arrest. Image guidance can help improve CPR quality by optimizing hand location.

Optimization of CPR quality is therefore a priority. Although only approximately 20% of patients with IHCA have an initial shockable rhythm, rapid defibrillation is associated with improved outcomes for these patients. Data supporting the efficacy of medications during IHCA are sparse. Current guidelines recommend the use of epinephrine and amiodarone, both of which improve short-term outcomes in OHCA, but there is limited evidence supporting substantial neurological improvement when these medications are used. Given the differences between IHCA and OHCA, especially with the much earlier administration of drugs in the in-hospital setting, it is unclear whether findings from studies of OHCA apply to IHCA. For in-hospital events, early administration of epinephrine in patients with a non-shockable rhythm is associated with better outcomes. ACLS can be modified in response to image guidance during IHCA providing potential to improve outcomes.

As ultrasound technology has evolved and improved in the recent past, several devices have appeared on the market. Essential companies include Philips, Sonosite, MindRay, GE, and Butterfly IQ. These companies provide both portable, mobile, handheld and roller machines that can be rapidly deployed at the bedside for evaluation of cardiac function. Most hospitals are now leaning on image guidance for echocardiography peri-arrest however evidence is equivocal. It makes logical clinical sense that imaging the organ of dysfunction during cardiac arrest would lend to improved outcomes, however it may come at a cost of ACLS interference, misdiagnosis, missed diagnosis and several other issues that remain to be researched, clinically investigated, and well vetted. However, due to the rapid use and increase in availability of ultrasound, it is now ever present at the bedside. Ultrasound guidance in vascular access is now ubiquitously used from a safety and efficacy standpoint.

However, transthoracic and transesophageal echocardiography have steep learning curves and often require advanced training. Both transthoracic and transesophageal echocardiography have specific board certifications that certify the level of competence necessary to interpret these exams. Future directions in ultrasound technology include the recently FDA approved Caption AI software which automates the image capturing and labeling of the cardiac structures. Applications of this mimic the development of other tools in medicine such as the automated external defibrillator (AED) and the electrocardiogram (EKG) machine which now interpret EKG rhythms and make diagnoses based on internal settings and programming.

2.2.2 Clinical Significance

The evidence to support RescueTEE comes from research that highlights the positive utilization of image guidance to identify the cause of IHCA, to help change management during intra-arrest ACLS, and to help improve clinical outcomes in particular survival. Thus far several clinical studies have been completed using RescueTEE and RescueTTE. In August 2020 the Journal of American College of Cardiology (JACC) published an excellent summary that demonstrates the rationale and current state of evidence for using TEE during IHCA¹². Table 1 briefly summarizes the current state of evidence for use of RescueTEE for IHCA. RescueTEE has been found to be useful for diagnostic and therapeutic guidance.

Table 1
Current observational data on in vivo use of RescueTEE.

First Author, Year	# Patients Location Study Design	Key Findings
Redberg, 1993 ¹³	20 ED Prospective Observational	Feasible and useful during intra-arrest. Cardiac pumping effectiveness
Van Der Wouw, 1997 ¹⁴	48 ED/Wards Prospective Observational	Diagnostic accuracy of TEE resuscitation
Lin, 2006 ¹⁵	10 OR Prospective Observational	TEE found to be impactful in identifying cause of arrest
Memtsoudis, 2006 ¹⁶	22 OR Retrospective Observation	TEE found to provide diagnostic information
Arntfield, 2016 ¹⁷	37 ED Retrospective Observational	TEE found clinical impactful to establish etiology of arrest
Teran, 2019 ¹⁸	33 ED Prospective Observational	TEE found to be feasible in the emergency room setting of OHCA
Fair, 2019 ¹⁹	12 ED Retrospective Observational	TEE guided pulse checks found to shorter compared to TTE guided checks
Catena, 2019 ²⁰	19 ED Retrospective Observational	Association between LVOT opening and ROSC

First Author, Year	# Patients	Key Findings
	Location	
	Study Design	
Fair, 2019 ²¹	25	Intra-arrest TEE feasible and useful for ECMO
	ED	
	Retrospective Observational	

Image guidance has been demonstrated to help augment ACLS in particular with pulse checks during CPR. The American Heart Association (AHA) guidelines for treating cardiac arrest are based on information from the pulse check and rhythm analysis to guide treatment, both of which have been shown to be error prone. In some studies, the accuracy of the pulse check has been as low as 15% when limited to the 10 seconds permitted for a pulse check.²² Multiple studies have shown discrepancy when comparing the rhythm observed by electrocardiogram (ECG) with that observed by echocardiography, with one study finding that 35% of patients thought to be in asystole had coordinated cardiac contractility.²³

There are two modalities for cardiac imaging; transthoracic and transesophageal echocardiography. Transthoracic echocardiography is an imaging modality that can be performed from the chest wall and abdomen and allows for imaging of the heart and lung structures. Recently, the REASON Trial by Gaspari et al. in 2017 assessed 225 patients in PEA cardiac arrest with cardiac activity on TTE during OHCA. They concluded that TTE guidance that identified organized cardiac activity that was treated with continuous adrenergic intervention resulted in better survival. They therefore concluded that TTE could help identify a subset of patients in PEA that may respond differently to ACLS interventions.²⁴ This study, although not utilizing the advantages of TEE, which as listed before includes non-interference with chest compressions, improved image quality, continuous monitoring, therapeutic guidance, etc., was able to demonstrate improved survival. Based on this data and evidence given that RescueTEE, an imaging modality superior to TTE and the outcomes data from the REASON Trial we hypothesize that RescueTEE would provide an even greater survival benefit during IHCA.

2.2.3 Supporting Science - Animal Studies

Rudikoff 1980²⁵

Background: Despite the widespread clinical application of cardiopulmonary resuscitation (CPR), the mechanism responsible for blood flow during this maneuver remains undefined, although it has been assumed that blood is squeezed from the heart by direct compression of the sternum. We studied the hemodynamics of CPR in 15 arrested dogs. **Findings:** During chest compression, pressures in the left ventricle, aorta, right atrium and pulmonary artery were essentially identical. These pressures were also equal to the intrathoracic pressure as estimated by an esophageal balloon catheter. Unequal transmission of pressures to the extrathoracic arterial and venous system resulted from collapse of the great veins at the thoracic outlet as intrathoracic pressures rose. This phenomenon gave rise to a peripheral arteriovenous pressure gradient and antegrade flow. When intrathoracic pressure was increased by maintaining the lungs fully inflated during chest compression, aortic systolic pressure rose from 27.3 +/- 4.0 mm Hg to 58.4 +/- 7.9 mm Hg ($p < 0.001$) and carotid blood flow increased from 9.0 +/- 2.2 ml/min to 28.6 +/- 5.9 ml/min ($p < 0.001$). Increasing the intrathoracic pressure by tightly binding the abdomen to prevent paradoxical diaphragmatic motion during chest compression also resulted in a rise in aortic systolic pressure, from 29.4 +/- 3.2 to 57.7 +/- 7.7 mm Hg ($p < 0.001$), and an increase in carotid blood flow, from 14.5 +/- 8.1 ml/min to 32.3 +/- 9.7 ml/min ($p < 0.005$). It

appears that pressure generation and blood flow during CPR in the dog result from a generalized rise in intrathoracic pressure, not from direct cardiac compression. Maneuvers that raise the intrathoracic pressure can dramatically increase carotid blood flow during CPR.

Urbanowicz 1990²⁶

Background: The purpose of this study was to determine whether the pressure produced by contact between a transesophageal echocardiography (TEE) probe and the esophagus was sufficient to cause esophageal damage. The authors studied the effects of sustained contact and associated surface pressure on the esophagus by a TEE probe in anesthetized dogs and humans. Contact pressure between the tip of the probe and the esophageal wall in dogs was measured using a previously described flat balloon of Silastic fitted to the end of a TEE probe and the recording system calibrated with a mercury manometer. **Findings:** In the dog studies, the probe was inserted, maximally flexed, and its position fixed for 4, 6, 8, and 12 h. The maximum surface pressure generated by contact between a probe and the esophageal wall was 10 mmHg. Subsequent pathologic studies failed to reveal either gross or microscopic evidence of tissue damage. The same system was used in short-term patient studies with the surface contact pressure transducer connected to a Camino Catheter 420 Digital Pressure Monitor. In five of six patients contact pressure was less than 17 mmHg despite maximal rotation of the TEE controls. However, one of the six patients developed very high contact pressure, up to 60 mmHg, between the probe and the esophagus. This patient had no history of esophageal disease but did have intrathoracic pathology.

2.2.4 Supporting Science – TTE Clinical Studies

Flato 2015²⁷

Background: Transthoracic echocardiography (TTE) during cardiopulmonary arrest (CPA) has been studied in victims of cardiac arrests. Our objective was to evaluate the feasibility and usefulness of TTE in victims of cardiac arrest with non-shockable rhythms hospitalized in intensive care units (ICUs). **Methods:** This prospective and observational cohort study evaluated ICU patients with CPA in asystole or pulseless electrical activity (PEA). Intensivists performed TTE during intervals of up to 10 seconds as established in the treatment protocol. Myocardial contractility was defined as intrinsic movement of the myocardium coordinated with cardiac valve movement. PEA without contractility was classified as electromechanical dissociation (EMD), and with contractility as pseudo-EMD. The images, the rates of return of spontaneous circulation (ROSC) and the survival upon hospital discharge and after 180 days were evaluated. **Results:** A total of 49 patients were included. Image quality was considered adequate in all cases and contributed to the diagnosis of CPA in 51.0% of the patients. Of the 49 patients included, 17 (34.7%) were in asystole and 32 (65.3%) in PEA, among which 5 (10.2%) were in EMD and 27 (55.1%) in pseudo-EMD. The rates of ROSC were 70.4% for those in pseudo-EMD, 20.0% for those in EMD, and 23.5% for those in asystole. Survival upon hospital discharge and after 180 days occurred only in patients in pseudo-EMD (22.2% and 14.8%, respectively). **Conclusions:** TTE conducted during cardiopulmonary resuscitation in ICU patients can be performed without interfering with care protocols and can contribute to the differential diagnosis of CPA and to the identification of a subgroup of patients with better prognosis.

Gaspari 2016²⁸

Background: Point-of-care ultrasound has been suggested to improve outcomes from advanced cardiac life support (ACLS), but no large studies have explored how it should be incorporated into ACLS. Our aim was to determine whether cardiac activity on ultrasound during ACLS is associated with improved survival. We conducted a non-randomized, prospective, protocol-driven observational study at 20 hospitals across United States and Canada. Patients presenting with out-of-hospital arrest or in-ED arrest with pulseless electrical activity or asystole were included. An ultrasound was

performed at the beginning and end of ACLS. The primary outcome was survival to hospital admission. Secondary outcomes included survival to hospital discharge and return of spontaneous circulation. **Results:** 793 patients were enrolled, 208 (26.2%) survived the initial resuscitation, 114 (14.4%) survived to hospital admission, and 13 (1.6%) survived to hospital discharge. Cardiac activity on US was the variable most associated with survival at all time points. On multivariate regression modeling, cardiac activity was associated with increased survival to hospital admission (OR 3.6, 2.2-5.9) and hospital discharge (OR 5.7, 1.5-21.9). No cardiac activity on US was associated with non-survival, but 0.6% (95% CI 0.3-2.3) survived to discharge. Ultrasound identified findings that responded to non-ACLS interventions. Patients with pericardial effusion and pericardiocentesis demonstrated higher survival rates (15.4%) compared to all others (1.3%). **Conclusion:** Cardiac activity on ultrasound was the variable most associated with survival following cardiac arrest. Ultrasound during cardiac arrest identifies interventions outside of the standard ACLS algorithm.

2.2.5 Supporting Science – TEE Clinical Studies

Fair 2019 ²⁹

Objective: Point-of-care ultrasonography provides diagnostic information in addition to visual pulse checks during cardiopulmonary resuscitation (CPR). The most commonly used modality, transthoracic echocardiography, has unfortunately been repeatedly associated with prolonged pauses in chest compressions, which correlate with worsened neurologic outcomes. Unlike transthoracic echocardiography, transesophageal echocardiography does not require cessation of compressions for adequate imaging and provides the diagnostic benefit of point-of-care ultrasonography. To assess a benefit of transesophageal echocardiography, we compare the duration of chest compression pauses between transesophageal echocardiography, transthoracic echocardiography, and manual pulse checks on video recordings of cardiac arrest resuscitations. **Results:** Transesophageal echocardiography provided the shortest mean pulse check duration (9 seconds [95% confidence interval {CI} 5 to 12 seconds]). Mean pulse check duration with transthoracic echocardiography was 19 seconds (95% CI 16 to 22 seconds), and it was 11 seconds (95% CI 8 to 14 seconds) with manual checks. **Conclusion:** Our study suggests that pulse check times with transesophageal echocardiography are shorter versus with transthoracic echocardiography for ED point-of-care ultrasonography during cardiac arrest resuscitations, and further emphasizes the need for careful attention to compression pause duration when using transthoracic echocardiography

Catena 2019 ²⁰

Background: Survival after cardiac arrest depends on adequate cardiopulmonary resuscitation (CPR). Manual or mechanical external chest compression may be ineffective to restore circulation: structures subjected to external chest compression may differ in forces transfer to intrathoracic structures due to anatomic characteristics and physiological changes. This clinical study aims to assess the association of transesophageal findings during CPR and successful resuscitation. **Methods:** Retrospective cohort study. Transesophageal assessment of right ventricular fractional area change, right ventricular outflow tract fractional shortening, left ventricular volumes, ejection fraction, and aortic diameters were performed in refractory out-of-hospital cardiac arrest patients admitted to emergency department for extracorporeal CPR. **Results:** 19 patients were analyzed. 15 of 19 patients (79%) received venous-arterial extracorporeal membrane oxygenation support. Resuscitation was successful with return of spontaneous circulation or electromechanical activity in 7 patients (group-SUXX) and failed in 12 patients (group-FAIL). 6 patients (32%) were alive at 24 h from the cardiac arrest, one patient (5%) survived to hospital discharge. Left ventricular outflow tract (LVOT) was open during CPR in all patients in group-SUXX and in 1 patient in group-FAIL (p 0.0002). None of the patients with closed LVOT had successful resuscitation. Patients in group-SUXX had a higher ejection fraction (p 0.03), ascending aortic diameter (p 0.04), and survival rate than those in group-FAIL (p 0.015). In a multiple variable Cox's proportional model LVOT opening was the only variable associated with successful resuscitation. **Conclusions:**

Transesophageal echocardiography can be useful in the emergency setting of cardiopulmonary arrest for discriminating between successful and failing resuscitation.

Arntfield 2018¹⁷

Objective: Critical care echocardiography has become an integral tool in the assessment and management of critically ill patients. Critical care transesophageal echocardiography (TEE) offers diagnostic reliability, superior image quality, and an expanded diagnostic scope to transthoracic echocardiography. Despite its favorable attributes, TEE use in North American intensive care units (ICUs) remains relatively undescribed. In this article, we seek to characterize the feasibility, indications, and clinical impact of a critical care TEE program. **Methods:** Retrospective, observational study. Setting: Tertiary care, academic critical care program consisting of 2 hospitals in Ontario, Canada. Participants: Consecutive critical care TEE examinations on ICU patients performed between December 2012 and December 2016. **Results:** Consecutive critical care TEE studies on ICU patients from December 1, 2012, to December 31, 2016, were reviewed. The TEEs performed on cardiac surgery patients and those without reports were excluded. Examination details, including indications, complications, examination complexity (number of views, Doppler techniques), and clinical recommendations were aggregated and analyzed. Two hundred seventy-four TEE studies were performed by 38 operators. Common indications for TEE studies were hemodynamic instability (45.2%), assessment for infective endocarditis (22.2%), and cardiac arrest (20.1%). A change in patient management was proposed following 79.5% of TEE studies. Thirty-eight percent of TEE studies were performed during evening hours or on weekends. There were no mechanical complications. **Conclusions:** Our observational data support intensivist-performed TEE as being safe and therapeutically influential across a broad range of indications. Our program's demonstrated feasibility and impact may act as a model for TEE adoption in other North American ICUs.

Markin 2014⁵

Background: Review the findings and use of rescue echocardiography performed by the Division of Perioperative Echocardiography and its impact on patient management. Design: Retrospective observational study. Setting: Single institution, tertiary care hospital. Participants: 364 consecutive rescue echocardiograms in the perioperative setting. Interventions: Rescue transesophageal or rescue transthoracic echocardiography. **Results:** Of a total of 1,675 perioperative echocardiograms performed in a 28-month period, 364 (21.8%) were rescue studies. Of these, 95.9% were transesophageal and 4.1% were transthoracic. Location at time of rescue echocardiography was intraoperative (55.5%), postoperative (44.2%), and preoperative (0.3%). No single diagnosis predominated the intraoperative or postoperative environment, and the frequency of common etiologies did not allow for assumption. There was a change in management for 214 patients (59%) as the result of findings. The methods used in performing rescue echocardiography at the authors' institution are reported. **Conclusions:** The heterogeneity of diagnoses and the frequency with which rescue echocardiography changed management further supports the growing body of evidence that the hemodynamically unstable perioperative patient benefits from its use.

Memtsoudis 2006¹⁶

Background: According to guidelines established by the American Society of Anesthesiologists and the Society of Cardiovascular Anesthesiologists, life-threatening hemodynamic disturbances are classified as a category I indication for the intraoperative use of transesophageal echocardiography (TEE). However, the usefulness of TEE during intraoperative cardiac arrest and its impact on patient management have not been rigorously investigated. **Methods:** Using our departmental TEE database, we identified a population of 22 patients who underwent noncardiac surgical procedures and experienced unexpected intraoperative hemodynamic collapse requiring the initiation of Advanced Cardiac Life Support procedures between the time of induction of general anesthesia and the termination of the

surgical procedure. Results of TEE examinations, patient records, detailed operative records, and outcome of patients were reviewed for the utility of TEE to diagnose the etiology of the hemodynamic collapse. Furthermore, the impact on subsequent patient management was evaluated. **Results:** A primary suspected diagnosis of the underlying pathological process was established in 19 of 22 patients with TEE, including 9 with thromboembolic events, 6 with acute myocardial ischemia, 2 with hypovolemia, and 2 patients with pericardial tamponade. A definitive diagnosis could not be made in 3 patients with TEE. In 18 patients, TEE guided specific management beyond implementation of Advanced Cardiac Life Support protocols, including the addition of surgical procedures in 12 patients. Fourteen patients survived to leave the operating room, and 7 of these patients were eventually discharged from the hospital. **Conclusion:** Thus, TEE may provide additional diagnostic information in patients with intraoperative cardiac arrest and may directly guide specific, potentially life-saving therapy.

Van Der Wouw 1997¹⁴

Objectives: We sought to establish the diagnostic accuracy of transesophageal echocardiography (TEE) during cardiopulmonary resuscitation. Because of its bedside diagnostic capabilities, excellent cardiac images and lack of interference with resuscitation efforts, TEE is ideally suited to determine the cause of a circulatory arrest that is not due to severe arrhythmia. However, the diagnostic accuracy of TEE during resuscitation is unknown. **Methods:** TEE was performed in patients with prolonged circulatory arrest. The TEE diagnoses were compared with diagnoses from autopsy, surgery and clinical follow-up. **Results:** Of the 48 study patients (29 male, 19 female, mean age 6 SD 61 6 20 years), 28 had an in-hospital cardiac arrest and 20 an out-of-hospital onset of arrest. Forty-four patients eventually died; four survived to discharge. The diagnoses made with TEE were cardiac tamponade (n=6), myocardial infarction (n=21), pulmonary embolism (n=6), ruptured aorta (n=1), aortic dissection (n=4), papillary muscle rupture (n=1), other diagnosis (n=2) and absence of structural cardiac abnormalities (n=7). A definite diagnosis from a reference standard was available in 31 patients. The TEE diagnosis was confirmed in 27 of the 31—by postmortem examination (n=19), operation (n=2), angiography (n 5 2) or clinical course (n=4). In the other four patients the TEE diagnosis proved incorrect by postmortem examination. The sensitivity, specificity and positive predictive value of TEE were 93%, 50% and 87%, respectively. In 15 patients (31%), major therapeutic decisions were based on TEE findings. **Conclusions:** TEE can reliably establish the cause of a circulatory arrest during cardiopulmonary resuscitation.

Redberg 1993¹³

Background: There are two competing theories of the mechanism of yimblood flow during cardiopulmonary resuscitation. The "cardiac pump" theory postulates that blood flows because the heart is squeezed between the sternum and the spine. The "thoracic pump" theory postulates that blood flows from the thorax because intrathoracic pressure exceeds extrathoracic vascular pressure and that flow is restricted to the venous-to-arterial direction because of venous valves that prevent retrograde flow at the thoracic inlet. To determine which mechanism is operative during actual cardiopulmonary resuscitation, 20 patients were imaged with transesophageal echocardiography during resuscitation. **Methods:** Transesophageal two-dimensional and pulse Doppler echocardiography was begun within 7 minutes of initiation of cardiopulmonary resuscitation. **Results:** In the 18 patients who could be analyzed, the mitral valve opened during the release phase (diastole) and closed during the compression phase (systole) of cardiopulmonary resuscitation. Mitral velocity-time integral measured 8 ± 3 cm during diastole. There was compression of right and left ventricular cavities with significant reduction in measured left ventricular volume during cardiopulmonary resuscitation. In five patients, mitral regurgitation was present. **Conclusions:** Transesophageal echocardiography performed during actual cardiopulmonary resuscitation showing mitral valve opening during cardiac release, reduction of ventricular cavity size with compression, and atrioventricular regurgitation support the cardiac

pump theory of cardiopulmonary resuscitation. This study demonstrates the feasibility and usefulness of transesophageal echocardiography during cardiopulmonary resuscitation.

2.2.6 Public Health Benefits – Cardiac Arrest

IHCA has a low survival rate and directly impacts 290,000 patients in the United States year. Individuals who are not neurologically intact and survivors of IHCA can impose healthcare burden on communities. We anticipate that this trial will increase neurologically intact survival alleviating the burden posed by neurologically deficient survivors. IHCA patient management is further complicated by the fact that standard clinical paradigms such as door to balloon time and VT/VF direct to catheterization lab pathways do not exist as compared to its OHCA counterpart. This can result in delayed care for IHCA because the usual care pathway involves: first transfer to an ICU then management of the cause of arrest. The knowledge gained from the ReTEECA trial will make an important contribution to our ability to avoid a substantial number of deaths, with significant potential impact on national public health by returning neurologically intact patients to their communities. Point of care ultrasound has been a rapidly evolving field and has had a tremendous increase in utilization in the past decade. Many groups are now utilizing RescueTEE with limited evidence, in particular for guideline development. The ReTEECA trial will not only generate safety/effectiveness data but also shed light on the level of training required for a RescueTEE, thus providing an informed basis to justify broader national implementation and create a platform for a definitive Phase III clinical trial. IHCA disproportionately impacts minorities. We suspect that this trial will also help address disparities in outcomes. In particular using the EFIC mechanism we have targeted various communities, by deliberately including diverse populations for sampling.

2.3 Risk/Benefit Assessment

2.3.1 Known Potential Risks

IHCA has a very grim prognosis. Survival from CA drops to less than <1% after 45 minutes with conventional CPR and ACLS. There are some risks involved with placement of TEE probes. The primary risk is associated with esophageal tear, rupture, and perforation. The risk for this is less than 1 in 10,000.³⁰ This is the often quoted number given to patients when they are undergoing routine TEE in the outpatient setting. In addition, in this particular trial there is the risk of misinterpretation of the image findings which may result in change in code management. This risk will be extremely mitigated by having board certified echocardiographers performing examinations and the knowledge that TEE is generally considered a safe interventional procedure. Furthermore, blinded review of the images will be done for inter- and intra-rater reliability. This second read will provide clarity on the possibility of misdiagnosis and missed diagnosis.

After reviewing the literature closely, to-date there has not been any reported esophageal damage during chest compressions with in-situ TEE probe. Overall, we found many large studies involving the safety of TEE use in the echocardiography lab or in non-CPR situations. The earliest paper we found was published in 1991 by Daniel et al, who studied the safety of TEE in 15 cardiology divisions at different European institutions. From 1982 to 1988, the results of 10,419 TEE examinations were recorded; significant complications were documented for 18 of them. They included bronchospasm, hypoxia, non-sustained ventricular tachycardia, transient atrial fibrillation, third degree atrioventricular block, severe angina pectoris, and pharyngeal bleeding. One patient died from hematemesis stemming from an esophageal tumor. Overall, the study found TEE to be a low-risk procedure, having a complication rate of 0.18%.³¹ The safety of TEE has been surmised mostly from elective controlled procedures. We identified 11 articles that evaluated the use of TEE in the inpatient setting. They involved 127 patients in the in-patient setting. There were 7 patients from case reports, 84 patients from retrospective studies, and 36 patients from prospective reviews (small case reviews).^{5,32}

It is true the procedure risk rate during cardiac arrest is unclear at this time (the inherent risk of procedures generally increases during emergent situations); however we have obtained protocol from the Massachusetts General Hospital (MGH) where they have instituted a rescue TEE protocol for perioperative cardiac arrest.³³ In this particular IRB approved study they completed 48 TEE exams in a 2-year period. Twenty two percent of the RescueTEE were performed in the setting of cardiac arrest. They report no adverse outcomes to TEE probe placement or CPR. Based on Table and the literature cited the TEE the complication rate is likely low, so physicians should not be discouraged from using this modality during cardiac arrest if the scenario presents no contraindications. As mentioned ACEP has published practice guidelines for the use of TEE in ACLS.⁶ In total there are 55 publications, including case reports and case series, located in emergency room and operating room in the setting of cardiac arrests in 277 patients undergoing resuscitation with TEE. We found no reports of injuries or negative outcomes caused by the use of TEE during cardiac arrest.

During CPR patients undergo cardiac defibrillation. Patients routinely undergo defibrillation in the cardiac operating room and this has now been shown not to be a risk for RescueTEE. Another important safety question is whether one can defibrillate a patient while the transesophageal probe is in place. In 2008, Davis-Gome and Perkins published a letter in Resuscitation, asking that TEE probes be tested during transthoracic defibrillation.³⁴ It appears that no studies have been launched in response to that letter. However, in a case series, Blivas described 4 patients who were shocked while the TEE probe was in place, without complication.³⁵ We know that patients are routinely administered shock therapy in the operating room with transcutaneous pads or direct paddle defibrillation. No large reports of thermal injury have emerged in the last 40 years. Furthermore, no evidence of structural failure of the TEE probes have been found.

Esophageal intubation with the TEE probe is a procedure that does not require direct visualization. It is akin to placing a larger nasogastric tube. Therefore, chest compressions will not be stopped during ACLS for TEE probe placement. In the setting of difficult probe passage the TEE will be abandoned and the study aborted by the operator.

Since CPR and ACLS resuscitation are only recommended in patients with cardiac arrest, only patients who otherwise would be considered clinically dead are exposed to these risks. Risks of CPR itself include broken ribs, bruising and bleeding in the thoracic cavity, pneumothorax, airway dislodgement, hemopericardium, esophageal rupture and tear, and solid organ injuries. The additional risks imposed by TEE is significantly less than the intrinsic risks of CPR, ACLS and the actual clinical status of the patient, which is death.

We will mitigate risks of patient health information and clinical trial information by using PennVault and Penn CTMS which are secure platforms for research data entry. Furthermore, we will use secure online platforms housed within the University of Pennsylvania. All study personnel involved in data collection and analysis have taken the local IRBs required research training. In addition, subjects will be identified in the data base by a study number and links to specific identifiers will be kept in a separate secure location.

2.3.2 Known Potential Benefits

The most important and most singularly essential direct benefit to the patient will be neurologically intact survival and hospital discharge. There is accomplished several ways through RescueTEE guided ACLS. The key anticipated benefits of the study include immediate diagnosis of the cause of the IHCA, immediate intervention including changing medication management, fluid management, blood product administration, optimizing hand positioning over the acute myocardial infarction (AMI) during chest compressions, identifying and intervening on arrhythmias, and guiding therapeutic interventions including but not limited to tPA thrombolytic, pericardiocentesis and or management and placement of bedside MCS devices. Furthermore, early intervention includes activation of the cardiac catheterization

lab for AMI which typically has a door-to-balloon time of 30 minutes, the percutaneous embolism response team (PERT) for PE, and cardiothoracic surgery team in the setting of tamponade or acute aortic dissection. The direct results will be a life-saving at the individual patient level.

Immediate direct potential benefits include survival to the end of the cardiac arrest. Additional immediate benefits include diagnosis and treatment planning based on image guidance. Furthermore, direct immediate benefits include changes in the course of ACLS to help with instantaneous treatment and tailored treatment to the pathology causing the cardiac arrest. The long-term benefits include neurologically intact hospital discharge survival. Furthermore, as mentioned, there are direct public health benefits including less burden on communities and society with increased neurologically intact survival. Finally, health disparities can be illustrated and improved with image guidance and code changes.

Secondary benefits include clear guidance to the IHCA code team for therapeutic and diagnostic management. Confidence in the interventions based on image guidance. Conclusion of cardiac arrest and termination of efforts will be augmented by visual confirmation. Finally, baseline imaging will be established in which subsequent clinical examinations can be compared to.

Abstract SCA 2021: Diagnostic Evidence

Usman 2021:

To implement this POC RescueTEE guided ACLS strategy we instituted a pilot program to assess logistics, feasibility and gauge early outcomes at the Hospital of the University of Pennsylvania. A Redcap case record form (CRF) was created. A data entry portal was installed on all echocardiographer's cellphones at the University of Pennsylvania. Feedback was provided during a pilot period in order to create an informed data dictionary for future trials. A standardized 5-view RescueTEE algorithm was used. The TEE probe was transported to the code by technicians and the anesthesiologists performed the examination after a secure airway was obtained. A total of 20 exams in 12 weeks were analyzed during the trial run up. TEE exams started on average 7 minutes 33 seconds after code call. The therapeutic window was set at 10 minutes. We found 5 AMI, 2 PE, 1 aortic dissection, 11 acute RV dysfunction, 2 pericardial tamponade, and 1 acute valvular pathology. Accuracy was defined as the ability to rule in, rule out, or do both with RescueTEE. There were 3 lateral wall and 2 anterior wall MI. There was 1 clot in transit and 1 McConnell's sign for PE. The dissection was classified as type A. The valvular pathology was posterior mitral valve endocarditis. This helped define the degree of precision capable by RescueTEE. Images were reread after one week and there was 100% inter and intra-rater concordance which helped optimize a fixed process. RescueTEE have helped guide intervention including 7 VA ECMO cannulations, changing vasopressor medications, cardioverting 3 patients, and administering fluid and blood in 2 patients. No injuries occurred. After this pilot period a comprehensive case record form (CRF) was finalized for the ReTEECA trial.

2.3.3 Assessment of Potential Risks and Benefits

The current data demonstrates that the survival to discharge for in-hospital cardiac arrest is 23.9% in the year 2016.⁷ Due to extremely poor survival from cardiac arrest and the fact that the risk of complications for POC TEE are less than 0.01% presumed benefits of diagnosis, treatment, management changes, and potential therapy directed treatments such as tPA or MCS device placement extremely outweigh the high likelihood of death. Clinically, when the risks are heavily weighed by the benefits, in this case the timely diagnosis of a fatal event then the overwhelming preponderance is to proceed with the increased risk diagnostic test.

All risk of the TEE will be mitigated by placing the TEE in the therapeutic window. Minimizing the TEE to a total of 30 minutes. The TEE protocol has no anteflexion and retroflexion use which will limit the necessary contact of the probe to the esophagus. The benefit of the study is the early and prompt diagnosis of life-threatening pathology. In addition to the diagnosis there is the early intervention that will directly lead to life saving intervention at the point of care. Risk will be further mitigated by having advanced experienced clinicians administering the exam, monitoring for safety during and after exam, and judgement based on the cited articles from the current clinical practice and literature as cited.^{14–33,35–55}. All exams will be performed by cardiologists or cardiovascular anesthesiologists (MD) who are certified in transesophageal echocardiography.

3 Objectives And Endpoints

3.1 Primary Objective

The overall primary objective for the ReTEECA trial is to determine if survival to hospital discharge (SHD) is improved with 1) RescueTEE guided ACLS versus 2) conventional ACLS. In both arms patients will receive conventional ACLS and CPR with high quality chest compressions. After the completion of ACLS, RescueTEE patient outcomes will be tracked and recorded. De-identified patient information will include six types of data: past medical history, events surrounding the cardiac arrest, actions taken by health care professionals, peri-arrest presentation, peri-arrest interventions, and patient outcomes. Health care professional actions will include: ACLS medication administration, airway management, chest compressions, defibrillation, pacing, and other resuscitative interventions. Follow up data collected through chart review will focus on: survival at the end of the code determined by sustained ROSC, survival to the end of ICU discharge, and survival to the end of hospital discharge. In the case of death, follow up data on cause of death will be collected from chart review.

Primary Efficacy Endpoint:

Survival to Hospital Discharge (SHD)

Justification

Survival is the most widely accepted endpoint in CPR and cardiac arrest trials. Our trial is designed to evaluate the effect of imaging and RescueTEE guided ACLS in order to facilitate survival.

3.2 Secondary Objective

There are several secondary objectives. Most importantly, we aim to determine and quantify how TEE guided diagnosis and intervention after in-hospital cardiac arrest leads to improved survival to specific timepoints: 1) end of code, 2) ICU discharge, 3) 30-days post-arrest, 4) 3 months post arrest with neurologically intact survival 5) 6 months post arrest neurologically intact survival, and 6) at hospital discharge neurologically intact. Neurologically intact survival is defined as modified Rankin's Score (mRS) of 0-3 at each of the three time points 3 months, 6 months and hospital discharge.

Secondary Efficacy Endpoints:

Survival to end of Code

Survival to ICU discharge (variable length)

Survival to Neurologically intact Hospital Discharge (variable length)

Survival to 30 days post arrest (fixed length)

Survival to Neurologically intact 3 status month post arrest (fixed length)

Survival to Neurologically intact status 6 months post arrest (fixed length)

Justification

Many patients that survive from IHCA and are discharge continue to improve over three to six months. As such we need to assess their status at a later time to fully capture the neurological ability to improve in this population. Furthermore, as highlighted above hospital discharge and ICU discharge occur at variable time lengths which can lead to time bias, therefore fixed and variable length time points are used in the secondary analysis. Neurologically intact survival is defined as a modified Rankin Score (mRS) between 0-3. The first secondary outcome is to determine if RescueTEE during CPR can provide clinically meaningful diagnostic information in the management of IHCA.

Additional secondary endpoints include, ascertaining whether RescueTEE can provide clinically meaningful diagnoses intra-arrest and if that information can be used in the management of in-hospital arrest. Finally, secondary outcomes include the ability of RescueTEE to provide information that leads to therapeutic guidance or intervention for the code leader during intra-arrest situations. The intra-arrest TEE images will be used in attempt to diagnose the cause of arrest. There are several causes of cardiac arrest and TEE can be used to determine several of these causes. The RescueTEE CRF completed by the echocardiographer lists several diagnoses readily diagnosed with RescueTEE including: cardiac tamponade, left ventricle (LV) thrombus, right ventricle (RV) thrombus, fine ventricular fibrillation (VF), pulseless rhythm with echocardiographic evidence of motion (PREM) versus pulseless rhythm with echocardiographic evidence of standstill (PRES), acute myocardial infarction (AMI), aortic dissection, severe hypovolemia, severe global LV dysfunction, severe global RV dysfunction, and LV free wall rupture. (See CRF)

Finally, additional secondary outcomes will be to determine if RescueTEE can provide information that leads to therapeutic guidance or intervention for the code leader during arrest situations. Information regarding the interventions will include RescueTEE driven medication administration or procedural management. Interventions and decisions made on the RescueTEE will be performed by the Code MD. This outcome will also be recorded as a categorical variable as: fluid given, blood given, epinephrine given, shock advised for pulseless rhythm with echocardiographic evidence of motion (PREM), calcium given, pericardiocentesis performed, ECMO cannulation completed, thrombolytics administered, or chest compressions hand positioning changed, or chest compressions terminated. (See CRF)

3.3 Exploratory Objectives

There are several exploratory outcomes that the ReTEECA trial will hope to address. First the study will assess the feasibility of introducing TEE during IHCA. This will be determined by asking code leaders to fill up a form to reflect a qualitative feedback to see if TEE was useful in a subjective manner. We will also calculate the time from code to TEE probe insertion and also the time for total examination. Data will be collected on the technical challenges encountered with probe placement. Post-event images will be reviewed and quality will be assessed in terms of clarity, motion artifact, and reproducibility. We will record if the TEE interfered with chest compressions or ACLS as part of the data safety monitoring program.

With regards to the quantitative findings of TEE imaging we will record if ROSC occurred in a subset of patients who are experiencing cardiac arrest. If ROSC is obtained, defined as sustained ETCO₂ or sustained diastolic blood pressure

for greater than 1 minute, the relationship of ROSC to degree of post ROSC ejection fraction (EF), fractional area change (FAC), and regional wall motion abnormalities will be recorded. After the code, we will employ a blinded evaluator to completed post processing image analysis to analyze the echo images. We hope to define a new parameter in which a defined level of EF, FAC, or kinetic energy that is required in which a patient is more likely to have sustained ROSC. The images will be cross-referenced with the code documentation obtained from the EMR in a retrospective fashion. The data will be used to create sensitivity and specificity of ROSC based EF and sustained organized cardiac function. This will be compared against sustained ETCO2 or diastolic blood pressure on the arterial waveform.

We will also study RescueTEE and its ability to located the area of maximal impulse (AMI) for chest compressions. The echocardiographer will then use TEE to optimize hand positioning during cardiac arrest. This information will be recorded to study if there was a resultant change in ROSC based on optimal hand positioning.

A new concept that has emerged in the emergency medicine literature as a result of the REASON trial is called PseudoPEA. PseudoPEA is a pulse demonstrated on arterial waveform that was not detected through direct palpation with normal QRS electrocardiogram (EKG) findings. The REASON trial has led a new clinical entity described as pulseless rhythm with echocardiographic evidence of motion (PREM) and pulseless rhythm with echocardiographic evidence of standstill (PRES). We will assess the ability of RescueTEE to help differentiate and manage PRES versus PREM and outcomes based on therapeutic interventions. We will also try to understand if RescueTEE can be used to help predict those patients who will have increased likelihood of sustained ROSC.

Granular data will be collected in three major subgroups of patients. First, we will evaluate the utility of RescueTEE in MCS placement, device failure or manipulation. At the University of Pennsylvania ECMO consults prompt emergent evaluation for ECMO and cannulation at the bedside. We will assess if POC RescueTEE can help prevent indiscriminate cannulation during IHCA. We also will record data to determine if RescueTEE makes bedside and mobile cannulation safer.

RescueTEE will be used to help provide information for the indication and contraindication for eCPR and IHCA. Furthermore, Rescue TEE guidance will be used to assess if correct cannulation occurs. We will document if errors in cannulation occur during IHCA with and without RescueTEE. We hope to assess if POC TEE can help avoid inadvertent initiation of VV ECMO when attempting VA ECMO. Second, a subgroup analysis will be performed on IHCA for patient on MCS. There are several devices that have high failure rates including left ventricular assist devices (LVADs) and Impella devices. The Impella device, fraught with challenges in positioning, often requires repositioning at the bedside under echo guidance in the scenario of cardiogenic shock and arrest. We will study the utility of POC TEE for MCS device failure or calibration. The last specific last important sub-group we hope to evaluate is patients with distinct reversible pathology like pericardial tamponade or RV thrombus and the resolution of cause of IHCA and hemodynamic collapse with TEE guided pericardiocentesis or tPA/catheter directed therapies.

Finally, we will use the therapeutic intervention to see if RescueTEE decreases the time to intervention. For example, if the RescueTEE finds a MI then the time from diagnosis to catheterization lab, commonly known as the “door-to-balloon” time will be recorded. This will also be used for ECMO cannulation defined as the time from IHCA to on an MCS platform.

3.4 Table of Objectives, Endpoints and Justification

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
The overall primary objective for the ReTEECA trial is to determine if survival to hospital discharge (SHD) is improved with 1) RescueTEE guided ACLS versus 2) conventional ACLS .	Survival to Hospital Discharge	Survival is the most widely accepted endpoint in CPR and CA trials. Our trial is designed to evaluate the effect of imaging and RescueTEE guided ACLS in order to facilitate survival.
Secondary		

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
<p>To determine whether TEE guided diagnosis and intervention after in-hospital cardiac arrest leads to improved survival to specific timepoints: 1) end of code, 2) ICU discharge, 3) 30-days post-arrest, 4) 3 months post arrest with neurologically intact survival 5) 6 months post arrest neurologically intact survival, and 6) neurologically intact survival at hospital discharge.</p> <p>Intra-arrest Rescue TEE ability to diagnose pathology during ACLS</p> <p>Intra-arrest Rescue TEE ability to shape treatment and change management for ACLS</p>	<p>Survival to end of Code</p> <p>Survival to ICU discharge (variable length)</p> <p>Survival to Neurologically intact status at Hospital Discharge (variable length)</p> <p>Survival to 30 days post arrest (fixed length)</p> <p>Survival to Neurologically intact 3 status month post arrest (fixed length)</p> <p>Survival to Neurologically intact status 6 months post arrest (fixed length)</p> <p>To determine if RescueTEE guidance during CPR can provide clinically meaningful diagnostic information in the management of in-hospital arrest</p> <p>To determine if RescueTEE can provide information that leads to therapeutic guidance or intervention for the code leader during arrest situations</p>	<p>Many patients that survive from IHCA and are discharge continue to improve over three to six months. As such we need to assess their status at a later time to fully capture the neurological ability to improve in this population. Furthermore, as highlighted above hospital discharge and ICU discharge occur at variable time lengths which can lead to time bias, therefore fixed and variable length time points are used in the secondary analysis. Neurologically intact hospital discharge is defined as a modified Rankin Score (mRS) between 0-3. The first secondary outcome is to determine if RescueTEE during CPR can provide clinically meaningful diagnostic information in the management of IHCA.</p>
Tertiary/Exploratory		
Hypothesis driven questions based on subset RescueTEE	In a subset of patients who	Safety monitoring and subset analysis

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
guided ACLS including change in management for ACLS, Subpopulations such as mechanical circulatory support and also technical questions regarding image quality and reliability	<p data-bbox="527 153 716 548">obtain ROSC, defined by sustained EtCO₂ or sustained diastolic blood pressure, can TEE be used to correlate ROSC with kinetic energy as measured by ejection fraction</p> <p data-bbox="527 575 716 779">Can POC TEE be used to determine the optimal hand positioning for chest compressions</p> <p data-bbox="527 806 716 1199">Does optimization of hand positioning over the area of maximal impulse (AMI) during chest compressions based on TEE result in increased likelihood of ROSC</p> <p data-bbox="527 1226 716 1367">To determine if ECG findings of rhythms are correlated with TEE findings</p> <p data-bbox="527 1394 716 1682">To obtain qualitative feedback from the code leader regarding the usefulness of having POC TEE from a systems perspective</p> <p data-bbox="527 1709 716 1850">To determine if ECG findings of rhythms are correlated with TEE findings</p> <p data-bbox="527 1877 716 2016">To determine if RescueTEE decreased the time to intervention</p>	

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
	such as ECMO cannulation time or “door-to-balloon” time	
	To assess the feasibility and safety of TEE probe insertion during CPR	
	To assess the quality of imaging data obtained during the code from POC TEE	
	To see if RescueTEE delays ACLS	
	To determine the utility of POC TEE in eCPR and ECMO cannulation	
	To determine the utility of POC TEE in MCS failure cardiac arrest	

4 Study Design

4.1 Overall Design

4.1.1 Overall Design for Primary Hypothesis

Primary Hypothesis:

Based on our preliminary results we hypothesize that routine used of RescueTEE guided ACLS for IHCA will expedite diagnosis, treatment, intervention, and facilitate and identify reversible causes and significantly improve survival to hospital discharge and functional survival compared to standard ACLS.

Phase of the Trial:

This is a Phase II, single center, partially blinded, prospective, safety and efficacy pragmatic clinical trial

4.1.2 IHCA Setting

This study will focus on patients on patients who are admitted to the Hospital of the University of Pennsylvania. The University of Pennsylvania has currently 750 inpatient beds with an average of 2296 patients admitted per week. Typically, the average inpatient stay is 3.1 days. Data from the year 2018 from the Clinical Emergencies Committee

demonstrate that on average there are approximately 2.6 IHCA per week (0.6-4.8 IQR). This would equate to 2.6 ICHA per 2296 patients admitted per week ~ (1/1000). Approximately 35% of the ICHA occur in the critical care units which are a total of 150 of the 750 beds. Approximately 50% of IHCA occur in step-down units, floor beds or other hospital beds. The last 15% occur in hospital procedural areas including cardiac catheterization labs, radiology suites, gastroenterology suites, and holding areas.

The ReTEECA trial will include patients in any other location at the University of Pennsylvania defined as “in-patient” in which patients can experience cardiac arrest in the hospital. (See attached letter for study approval). In addition to enrolling traditional IHCA, the University of Pennsylvania has a unique set of circumstances that makes it challenging to strictly define IHCA. Typically, IHCA is defined as the lack of a pulsatile rhythm in a patient with or without cardiac standstill. For this study we will also include a specific subset of patients that are not routinely encountered in the general hospital setting outside of the quaternary medical center; namely mechanical circulatory support (MCS) patients and those patients that are at extreme physiologic spectrums. Any patient with a mechanical circulatory support device or evaluation for extracorporeal membrane oxygenation (ECMO) placement will also meet criteria to be eligible for the study – due to the inability to bin these patients into strictly IHCA and the nature of the definition of IHCA. This is a select few patients which will be also included in the broader IHCA group of patients. Data obtained from the CTICU, Rhoads 5 SICU and MCS services at the University of Pennsylvania demonstrate there are approximately 1-5 (Mean 2.6 IQR 0.6-4.8) IHCA patients per week that potentially can be enrolled into the ReTEECA trial. We estimate to collect a total of 100-125 RescueTEE studies per year from in-hospital cardiac arrest.

Regarding MCS, in particular for this IRB submission, the MCS consults average approximately 0-5 per week. On average in the CTICU there are seven to ten active MCS devices ranging from intra-aortic balloon pumps (IABP), left ventricular assist devices (LVADs), right ventricular assist devices (RVADs), Impella, venovenous (VV) ECMO, venoarterial (VA) ECMO, Avalon catheters, and RA-PA catheters. Each one of these devices carries an intrinsic risk for failure, suck down events, and catheter malpositioning resulting in IHCA. Not all of these situations will result in TEE placement; however, these cases will be eligible for the study.

The study arms: Echo CPR (RescueTEE) ACLS versus Conventional ACLS.

4.1.3 Study Clinicians

The critical care anesthesiology and cardiovascular anesthesiology fellows who rotate through the CTICU on a monthly basis will administer the RescueTEE protocol with ICU attending supervision. These fellows during their clinical year sit for the National Board of Echocardiographer (NBE) board examination, typically in January for the ICU fellows and August for the cardiac fellows; and therefore, are within their scope of practice to perform echocardiography. The attending staff supervision will be provided by the cardiovascular anesthesiology attendings in the CTICU who are available for the study at all times. The use of RescueTEE in the perioperative period is within the scope of practice of CV anesthesiologists and ICU intensivists who are board certified or eligible by the NBE. CV anesthesiologists and intensivists who have completed training in POCUS RescueTEE and maintain competency standards to perform POC RescueTEE will be part of the study design.

RescueTEE MD: Board Certified CV and ICU Anesthesiologists, Board Eligible ICU and CV Anesthesiology Fellows with Attending supervision.

4.1.4 Study TEE Protocol

We will use a recently published, validated and publicly available protocol from the Massachusetts General Hospital for RescueTEE. This sequence consists of 5 of the standard views included in both the American Society of

Anesthesiologists/Society of Cardiovascular Anesthesiologists basic and comprehensive TEE examinations.³³ These views were chosen because they are relatively easy to obtain, simple to interpret with some background in TEE, and focus on structures that are most frequently implicated in serious hemodynamic compromise. The purpose of rescue TEE is to swiftly recognize serious cardiac pathology, not undertake a comprehensive echocardiographic evaluation, a goal that is bolstered by using this simple sequence.

Staudt 2018: Development of a Rescue Echocardiography Protocol for Noncardiac Surgery Patients Anesthesia and Analgesia ³³

Objectives

... we developed a modified TEE examination sequence to promote a focused, expeditious examination. This sequence consists of 5 of the standard views... These views were chosen because they are relatively easy to obtain, simple to interpret with some background in TEE, and focus on structures that are most frequently implicated in serious hemodynamic compromise. The purpose of rescue TEE is to swiftly recognize serious cardiac pathology, not undertake a comprehensive echocardiographic evaluation, a goal that is bolstered by using this simple sequence.

Methods

Billing data were used to compile a list of all intraoperative TEEs that were performed by RES in noncardiac procedures over a 22-month period from May 1, 2015 to March 31, 2017. Anesthesia care records were reviewed, and patients were classified as undergoing either a rescue or monitoring examination. Only those patients who had a rescue examination performed were included in further data analysis. Medical records, anesthesia care records, and echocardiographic reports were analyzed. An intervention qualified as a change in management if one of the following criteria was met

1. Alteration in medication administration.
2. Change in fluid management strategy.
3. New or altered surgical procedure.
4. Escalation in the level of care, such as intensive care unit admission.

Results

Over the study period, we performed 48 intraoperative rescue TEEs. In the first 11 months, 14 examinations were performed. This number increased to 34 examinations over the next 11 months as awareness of the RES increased. Rescue TEE was used more frequently but not exclusively in older patients (69% of patients >60 years of age) ... The most common indication for rescue TEE was refractory hypotension (47.9%). This was followed by cardiac arrest (22.9%) and ST changes (10.4%). Arrhythmias and hypoxia made up a significantly smaller proportion of requests (Table). In some instances, patients were demonstrating multiple signs of hemodynamic instability (ie, ST changes and refractory hypotension). This was the most common conclusion, seen in 23 of 48 studies (47.5%). Hypovolemia was diagnosed by visualizing a small, hyperdynamic ventricle with inadequate diastolic filling and low estimated cardiac output, seen in 10 of 48 examinations (20.8%). Valvular abnormalities were only included if they demonstrated at least moderate to severe pathology. Trivial regurgitation was frequently seen but was included in the normal examination group because this physiological finding has little potential to be the cause of hemodynamic instability. Within the valvular disease group, regurgitation was a significantly more common finding than stenosis. Ventricular failure could be left or right sided and included both acute failure and previously unknown chronic failure. Diagnosis of myocardial ischemia required the presence of regional wall motion abnormalities. Pulmonary embolism was only diagnosed if a

thrombus was directly visualized in the right ventricular outflow tract or pulmonary artery. The patients (72.9%) had a change in management after rescue TEE, and some had multiple interventions. Significant interventions included emergent pulmonary thromboendarterectomy, initiation of extracorporeal membrane oxygenation, and case cancellation. It is also important to note that 47.5% of patients had a normal examination; however, only 27.1% had no change in management. This finding suggests that a negative examination may also be helpful in guiding management.

4.1.5 Image Storage and review

All TEE images will be stored locally on the echo machine and then uploaded to a local drive for a wet read. All RescueTEE will have a RescueTEE case record form (CRF) completed at the time of examination (see 3.3 Study Measures). For the ReTEECA trial post processing and formal overread with CV Anesthesiology or Cardiology, if needed, will be completed after the code event by that department, usually within the next 1-3 business days. This will be in the setting of a clinical pathology that was found, significant enough that unblinding is necessary. TEE exams that are performed will be included in the departmental QA process and reviewed monthly. All patient information will be de-identified for clinical case conference. Selected cases will be queried for safety and process improvement in the CTICU safety report. RescueTEE quality project will advance improvement in early diagnosis, intervention and safety of bedside procedures will occur and will help guide further indications. Image review will also occur through the data monitoring and safety board created for the study.

4.2 Allocation to Interventional Group

When overhead code calls are placed at the Hospital of the University of Pennsylvania (HUP) the available CV anesthesiology fellow from the CTICU will travel with the TEE probe and TEE portable laptop to the code location. The study is randomized by month. Conventional ACLS without TEE guidance will be done on certain months while RescueTEE guided ACLS will be done on alternative months. The study will be performed as a convenience sampling methodology during the day time hours where the RescueTEE service will be provided only during fellow and attending availability for the duration of the study. CV Anesthesiology attending staff will be available for TEE supervision and review of the images. If the patient meets the criteria for the study the RescueTEE probe will be introduced and images obtained. The therapeutic window is defined as the time the code is called until the RescueTEE probe is placed. Due to the urgent nature and diminishing returns of POCUS RescueTEE during ACLS the therapeutic window is defined as 10 minutes from the start of the Code call. See EFIC for therapeutic window and exception from informed consent documentation and plan.

4.3 Study Measures

A CRF will be completed by the echocardiographer after the completion of the RescueTEE for IHCA

Study Form for Rescue TEE: The actual CRF can be found at: <https://redcap.link/ReTEECATrialUsman.Gutsche>

Study Form for Rescue TEE: See CRF Redcap Program attached.

4.4 Scientific Rationale for Study Design

The ReTEECA Trial will use a recently published and validated focused 5-view RescueTEE evaluation for patients with IHCA to obtain diagnostic and therapeutic information to aid in medical decision-making in a rapid fashion for those patients who are experiencing in-hospital arrest.¹ The indications for using a validated published RescueTEE protocol is to study the outcome effects of an effective intervention that is publicly available and apply this in a real world clinical scenario as a prospective trial. The goal of the study will be to study how RescueTEE information can help

guide the code leader for management decision-making and decrease IHCA mortality rates. We further hope to assess if TEE guidance of therapies or interventions can result in improved peri-arrest outcomes. This is an interventional prospective convenience sampled study looking at outcomes comparing RescueTEE image guided ACLS versus conventional ACLS.

4.5 Justification for Therapeutic Window

For complete details see EFIC protocol

Ideally, the RescueTEE exam should be completed as soon as the cardiac arrest occurs. However, the natural sequence of events that necessitates this to be an EFIC study to meet the therapeutic window criteria is the following: First an overhead cardiac arrest code call is placed. The RescueTEE team will then travel from the storage location of the TEE probe, currently in the cardiothoracic intensive care unit (CTICU), to the code location which is a variable distance in the hospital. Then based on the time it takes to secure the airway with an endotracheal tube by the anesthesia team and working through the indications and contraindication for RescueTEE for IHCA ReTEECA Trial the TEE probe will be deployed. This time can be variable. Data based on a time lapse study of CPR in 11,368 OHCA with 4023 ROSC patients and 905 patients with neurologically intact modified Rankin's Score (mRS) 0-3 survival the median CPR duration was 20 minutes. The average time for those who achieved ROSC was 13.5 minutes while those without ROSC was 23.4 minutes. Subjects with initial shockable rhythms and witnessed cardiac arrest were more likely to survive after prolonged ACLS which is defined as 30-40 minute of CPR with mRS 0-3 at discharge.³⁶

We therefore define the therapeutic window as the time from code call to TEE placement which should be less than 10 minutes from the initial code call. It is imperative to start the RescueTEE at the earliest time point possible which is defined as the time of cardiac arrest code call. This will allow for the maximum therapeutic benefit. The RescueTEE team intends to arrive at the patient bedside alongside the airway rapid response team because a secured airway is essential in ACLS management and required prior to the commencement of the study and placement of the TEE probe. The RescueTEE probe will remain indwelling for a total of 30 minutes or to the termination of CPR whichever is first. IHCA patients undergoing CPR are generally unconscious. Legally authorized representatives are often not available during the first 10 minutes of a code call, during treatment, stabilization and disposition of the patient. Since we are studying IHCA, which is frequently the first manifestation of cardiovascular disease, there is no way to prospectively identify individuals who are likely to become eligible for this trial.

4.6 End of Study Definition

The study team will be activated at the time that an IHCA call is made overhead through the central communication service of the hospital. The RescueTEE team will then arrive at the patient bedside and if the patient meets the listed inclusion criteria and the ACLS medicine code team agrees then the RescueTEE probe will be placed. We will record the time from code call to the time of TEE placement and from the time of TEE placement to the time of completion of the 5 RescueTEE views. We will also record the duration of the code and the duration that the TEE was deployed. The RescueTEE will remain indwelling during the duration on ACLS/CPR up to a total of 30 minutes after placement. The time from the code call to the time that the TEE is placed can be variable and is defined as the therapeutic window. The time from the start of the code to the time that the TEE placement should not be longer than 10 minutes. (See EFIC) Clinically, data demonstrates that each minute that passes the likelihood of ROSC after IHCA diminishes and is statistically significantly diminished after 40 minutes. Therefore, we seek to deploy the RescueTEE within 10 minutes of the cardiac arrest call. This time will logistically include activating the team, traveling to the code location, determining the inclusion and exclusion criteria and then successful placement of the probe and completing the exam. Once the TEE is in place the TEE will remain for 30 minutes or to the conclusion of the code whichever is shorter.

RescueTEE probes will be removed at the conclusion of the CPR event. Retrospective chart review will be completed for survival analysis.

After the initial Rescue TEE patients will remain enrolled by chart review and also screened for neurological function. Chart review, as highlighted in the schedule of activities will include follow up imaging review, conducted as clinically warranted. There will be no invasive intervention after the initial RescueTEE by the research team. Dedicated neurological assessment using the modified Rankin scoring will be completed at specific timepoints as highlighted above. The study data collection will end either upon death of the patient or after completion of the 6-month assessment in the survivors.

Details for Modified Rankins Scoring is as follows: (Adopted from Specification Manual for Joint Commission national Quality measures)

Blinded assessment of the mRS study endpoints will be accomplished as follows:

At hospital discharge, 3 months, and 6 months, a blinded evaluator will determine the mRS and CPC in-person or by telephone. All mRS scoring staff will be blinded to type of CPR received, either conventional-CPR or image guided-CPR. Evaluators will obtain certification from rankinscale.org. If the patient cannot be evaluated prior to hospital discharge, a blinded evaluator will acquire the mRS score and CPC classification within 2 weeks of hospital discharge by telephone or in-person during a follow up clinic visit. If the patient cannot be interviewed because of communication deficits or other limitations, an interview with the patient's caregiver is acceptable. A hospital translator will be used for non-English speaking patients.

Sources for scoring the mRS will be taken directly from the patient as well as augmented by data from progress notes, physical therapy notes, care transition notes, consultation notes, home health notes, logs from phone calls, and outpatient records. mRS is a 6-point disability scale with possible scores ranging from 0 to 5. A separate category of 6 is usually added for patients who expire. The Modified Rankin Score (mRS) is the most widely used outcome measure in stroke clinical trials. Standardized interviews to obtain a mRS score are recommended at 3 months (90 days) following hospital discharge.

Scoring is defined as follows

0: The patient has no residual symptoms

1: The patient has no significant disability; Able to carry out all pre-stroke activities

2: The patient has slight disability; unable to carry out all pre-stroke activities but able to look after self without daily help

3: The patient has moderate disability; requiring some external help but able to walk without the assistance of another individual.

4: The patient has moderately severe disability; unable to walk or attend to bodily functions without assistance of another individual.

5: The patient has severe disability; bedridden, incontinent, requires continuous care.

6: The patient has expired (during the hospital stay or after discharge from the hospital)

5 Study Population

5.1 Inclusion Criteria

The study will include a very specific patient population. It will include only patients who are experiencing IHCA*. The study is for any patient admitted to the Hospital of University of Pennsylvania. Secondly, there is a very unique and specific subgroup that will also be included for RescueTEE evaluation. This specific patient population group itself has a broader definition of IHCA due to the presence of MCS. Therefore, any patients who have mechanical circulatory support including left ventricular assist devices or patients who are being evaluated for extracorporeal membrane oxygenation (ECMO) support with IHCA will be eligible for the study enrollment. This includes all patients who experience cardiac arrest as an inpatient in the hospital. The interventional group is the patients undergoing image guided ACLS with Rescue TEE. The comparator group is patient with conventional ACLS for IHCA without RescueTEE.

*Note: including a subset of patients as noted with severe hemodynamic derangements and/or MCS.

- All patients greater than 18 years of age
- Intubated or permanent tracheostomy in situ
- Patients being actively intubated as part of ACLS
- In-hospital cardiac arrest

Exclusion Criteria

- DNR
- Unsecured airway
- Aspiration
- History of Tracheoesophageal injury
- History of Tracheoesophageal fistula
- Esophagectomy
- Active upper GI bleeding
- Esophageal Varices
- Ongoing hemoptysis
- Technically challenging TEE placement
- Pregnancy
- Opt-out bracelet

5.3 Duration of Study Participation

The study team will be activated at the time that an IHCA call is made overhead through the central communication service of the hospital. The RescueTEE team will then arrive at the patient bedside and if the patient meets the listed inclusion criteria and the ACLS medicine code team agrees then the RescueTEE probe will be placed. We will record the time from code call to the time of TEE placement and from the time of TEE placement to the time of completion of the 5 RescueTEE views. We will also record the duration of the code and the duration that the TEE was deployed. The RescueTEE will remain indwelling during the duration on ACLS/CPR up to a total of 30 minutes after placement. The time from the code call to the time that the TEE is placed can be variable and is defined as the therapeutic window. The time from the start of the code to the time that the TEE placement should not be longer than 10 minutes. (See EFIC)

Clinically, data demonstrates that each minute that passes the likelihood of ROSC after IHCA diminishes and is statistically significantly diminished after 40 minutes. Therefore, we seek to deploy the RescueTEE within 10 minutes of the cardiac arrest call. This time will logistically include activating the team, traveling to the code location, determining the inclusion and exclusion criteria and then successful placement of the probe and completing the exam. Once the TEE is in place the TEE will remain for 30 minutes or to the conclusion of the code whichever is shorter. RescueTEE probes will be removed at the conclusion of the CPR event. Retrospective chart review will be completed for some data extraction and survival analysis.

There will be no repeat RescueTEE performed after the initial RescueTEE. If a patient survives to ROSC and is subsequently admitted to the ICU, a formal TEE or TTE may be obtained by the admitting service. This is a clinical decision that is independent of the trial. Images and findings from any follow up imaging studies will be retrospectively chart reviewed collected as trial data as a comparator to the POCUS RescueTEE images. This “visit one” will only apply to a subset of patients that have ACLS/image guided ACLS performed, then survive the cardiac arrest, and then have formal TTE/TEE after the event by the ICU team.

5.4 Screen Failures

Eligibility and exclusion criteria for the ReTEECA trial are described in section 5.1 and 5.2 of this protocol. Some of the criteria will not be ascertainable at the time the RescueTEE team arrives to the IHCA due to the nature of the emergency and limited information. These potentially include the age greater than 18 in some cases, valid do-not-attempt-resuscitation (DNAR) orders, known pregnancy status, and other absolute contraindications such as recent esophageal surgery. Thus, some patients may be randomized to RescueTEE and then included in the rescue TEE arm dataset as a screening failure. We will include all data on such patients up to the point that their ineligibility is determined in the RescueTEE arm as intention to treat and this data will be used for analysis. Since no further high-risk intervention will occur after the code, patients will be informed of the procedure and consent for continued participation will be done. If the patient agrees to remain in the trial, follow up assessment will be done according to trial schedule. If the patient refuses to continue to participate in the trial, then data will remain in the trial up to the point of refusal per the FDA guidelines. There should be no screening failures in the conventional ACLS arm since this group will not have interventions during convention ACLS.

5.5 Strategies for Recruitment and Retention

This study will focus on patients who are admitted to the Hospital of the University of Pennsylvania. The University of Pennsylvania has currently 750 inpatient beds with an average of 2296 patients admitted per week. Typically, the average inpatient stay is 3.1 days. Data from the year 2018 from the Clinical Emergencies Committee demonstrate that on average there are approximately 2.6 IHCA per week (0.6-4.8 IQR). This would equate to 2.6 ICHA per 2296 patients admitted per week $\sim (1/1000)$. Approximately 35% of the ICHA occur in the critical care units which are a total of 150 of the 750 beds. Approximately 50% of IHCA occur in step-down units, floor beds or other hospital beds. The last 15% occur in hospital procedural areas including cardiac catheterization labs, radiology suites, gastroenterology suites, and holding areas.

The ReTEECA trial will include patients in any other location at the University of Pennsylvania defined as “in-patient” in which patients can experience cardiac arrest in the hospital. (See attached letter for study approval). In addition to enrolling traditional IHCA, the University of Pennsylvania has a unique set of circumstances that makes it challenging to strictly define IHCA. Typically, IHCA is defined as the lack of a pulsatile rhythm in a patient with or without cardiac standstill. For this study we will also include a specific subset of patients that are not routinely encountered in the general hospital setting outside of the quaternary medical center; namely mechanical circulatory support (MCS) patients and those patients that are at extreme physiologic spectrums. Any patient with a mechanical circulatory

support device or evaluation for extracorporeal membrane oxygenation (ECMO) placement will also meet criteria to be eligible for the study – due to the inability to bin these patients into strictly IHCA and the nature of the definition of IHCA. This is a select few patients which will be also included in the broader IHCA group of patients. Data obtained from the CTICU, Rhoads 5 SICU and MCS services at the University of Pennsylvania demonstrate there are approximately 1-5 (Mean 2.6 IQR 0.6-4.8) IHCA patients per week that potentially can be enrolled into the ReTEECA trial. We estimate to collect a total of 100-125 RescueTEE studies per year from in-hospital cardiac arrest. A total of 250 patients will be enrolled in the Echo ALCS arm and 250 in the conventional ALCS arm.

Regarding MCS, in particular for this submission, the MCS consults average approximately 0-5 per week. On average in the CTICU there are seven to ten active MCS devices ranging from intra-aortic balloon pumps (IABP), left ventricular assist devices (LVADs), right ventricular assist devices (RVADs), Impella, venovenous (VV) ECMO, venoarterial (VA) ECMO, Avalon catheters, and RA-PA catheters. Each one of these devices carries an intrinsic risk for failure, suck down events, and catheter malpositioning resulting in IHCA. Not all of these situations will result in TEE placement; however, these cases will be eligible for the study.

- Single Center Large Academic University based hospital
- In-patient Hospital Setting as defined by Utstein AHA ILCOR definitions:

Ambulatory/outpatient area; adult CCU; adult ICU; cardiac catheterization laboratory; delivery suite; diagnostic/intervention (other than catheterization laboratory); emergency department; general inpatient area; high dependency unit; operating room; post-anesthesia recovery room; rehabilitation; same-day surgical area; telemetry unit or step-down unit; Other (inpatient) Hospital specific²

- All patients with in-hospital cardiac arrest
- Exception from Informed Consent (EFIC) for interventional arm; post cardiac arrest consent and follow up for standard ACLS arm
- All entered study subjects or their legally authorized representative will have signed informed consent for continued participation in the trial and agreed to follow up assessment at 1, 3 and 6 months and hospital discharge. Contact information of the study subject, their significant other, and relevant additional contacts will be acquired prior to hospital discharge. One, three and 6-month evaluations will occur by telephone or in-person during clinic appointments.
- Patients who are recruited to the study will be at the POC during cardiac arrest. The proposal has been presented and approved by the HUP clinical emergencies committee (CEC) that oversees the code and rapid response teams. Team members are up to date regarding the objectives of the study. The cardiovascular anesthesiologists who will provide TEE at the POC will also provide oversight of the project. Due to the extreme urgency of the clinical TEE examination and the fact that the patients will be evaluated at the time of arrest consent will be assumed under emergency care. (See EFIC)
- A specific script, driven by the clinical emergencies committee at the University of Pennsylvania, has been written to provide timely and useful information during the image guided ACLS. (See attachment appendix 3)

6 Study Intervention

6.1 Study Intervention(s) Administration

6.1.1 Study Intervention Description

The ReTEECA trial is comparing image guided RescueTEE ACLS versus conventional ACLS. This intervention lasts up to 30 minutes of diagnostic imaging during IHCA. No treatment recommendations will be provided to the code team or critical care team outside of that 30 minutes. All surviving patients in the conventional ACLS and image guided RescueTEE ACLS will have their mRS scores determined at 3 months, and 6 months as well as at hospital discharge.

The CTICU team uses an FDA approved CX50 Philips machine and X8-2T probe. This device is housed in the CTICU and will travel to the IHCA when an overhead code is called. It is placed in a clean location and washed and prepared according to national hospital standards for probe processing and handling.

The Philips CX50 is a general purpose, software controlled, diagnostic ultrasound systems. Its function is to acquire ultrasound data and to display the data in various modes of operation. The CX50 CompactXtreme ultrasound system features PureWave crystal technology. With PureWave crystal technology, clinicians can rely on exceptional tissue detail, enhanced far field resolution, and the ability to image a wide variety of patients, including the technically difficult cases. The CX50 xMatrix system is the ideal choice for imaging critically ill patients. Its lightweight, small and highly mobile cart allows for easy maneuverability in the confined ICU and hospital environment. The X8 TEE probe, compatible with the CX50 machine, is also FDA approved for clinical use. This transesophageal probe is soft tipped and lightweight.

The device consists of two parts: the system console and the transducers. The system console contains the user interface, a display, system electronics and optional peripherals (ECG, printers), in addition to the physical knobs and buttons of the main control panel. The CX50 diagnostic ultrasound system is a compact, AC or battery powered, 128 – channel, diagnostic ultrasound imaging system. It is housed in a portable, laptop-style chassis. An optional cart is available that allows the user to place the laptop on the cart for a more mobile application. The removable transducers are connected to the system using a standard technology, multi-pin connectors. The modified CX50 uses standard transducer technology, and supports phased, linear, curved linear array, TEE, and non-imaging (pencil) probes. Clinical data storage consists of a local repository as well as off-line image storage via the network, DVR, DVD, and USB storage devices. The images are stored in industry-standard formats (e.g. JPEG, AVI, DICOM) and are intended to be readable using industry-standard hardware and software. On-line review of the images is available. Secure access tools are provided to restrict and log access to the clinical data repository according to HIPAA. No changes will be made to the machine.

University of Pennsylvania uses a Wi-Fi enabled imaging warehousing system called Syngo Cardiology Reader. The CX50 is link enabled and communicates with the server at the end of each exam to transmit images to the electronic medical record.

When overhead code calls are placed at the Hospital of the University of Pennsylvania (HUP) the available CV anesthesiologist from the CTICU will travel with the TEE probe and TEE portable laptop to the code location. The study will be randomized according to the scheme described in section 6.3. CV Anesthesiology attending staff will be available for TEE supervision and review of the images. If the patient meets the criteria and no exclusion criteria are found for the study the RescueTEE probe will be introduced and images obtained.

The TEE probe can be introduced blindly with neck palpation or with direct or video laryngoscopy. This will be determined by the physician (MD) performing the TEE and left to their clinical discretion. TEE probes will be placed by anesthesiologists with advanced airway skills capable of managing all airway and oropharyngeal pathologies. The therapeutic window is defined as the time the code is called until the RescueTEE probe is placed. Due to the urgent nature and diminishing returns of POCUS RescueTEE during ACLS the therapeutic window is defined as 10 minutes

from the start of the code call. See EFIC for therapeutic window and exception from informed consent documentation and plan.

6.1.2 Intervention Duration

Echocardiography Exposure: Patients who are in the echocardiography arm will receive RescueTEE guided ACLS for a maximum of 30 minutes. This study could not be conducted without the waiver of consent because legally authorized representatives are often not available during the first 10 minutes following the start of the cardiac arrest. The therapeutic window is defined as the first 10 minutes from the code call in which the RescueTEE will provide the maximum potential benefit to the patient. In clinical terms, scenarios including myocardial infarctions, pulmonary embolisms, and mechanical circulatory support placement must be addressed in the first 30 to 60 minutes of CPR. After this time frame the benefits of the therapeutic intervention degrade. Potential benefit of RescueTEE to the patient may be significantly reduced if it is not initiated within the therapeutic window of 10 minutes and indwelling for the first 30 minutes of the code. It may be too late to institute the therapeutic interventions based on the findings of the RescueTEE such as needing cardiac stenting or starting mechanical circulatory support if the TEE is placed at a later time point.

There will be no repeat RescueTEE performed after the initial RescueTEE. If a patient survives to ROSC and is subsequently admitted to the ICU, a formal TEE or TTE may be obtained by the admitting service. This is a clinical decision that is independent of the trial. Images and findings from any follow up imaging studies will be retrospectively chart reviewed collected as trial data as a comparator to the POCUS RescueTEE images. This “visit one” will only apply to a subset of patients that have ACLS/image guided ACLS performed, then survive the cardiac arrest, and then have formal TTE/TEE after the event by the ICU team.

There will be no repeat RescueTEE performed after the initial RescueTEE. If a patient survives to ROSC and is subsequently admitted to the ICU, a formal TEE or TTE may be obtained by the admitting service. This is a clinical decision that is independent of the trial. Images and findings from any follow up imaging studies will be retrospectively chart reviewed collected as trial data as a comparator to the POCUS RescueTEE images. This “visit one” will only apply to a subset of patients that have ACLS/image guided ACLS performed, then survive the cardiac arrest, and then have formal TTE/TEE after the event by the ICU team.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Acquisition and Accountability

Standard handling of the CX50 and X8-2T probes will be completed as per local policies. Device management will be provided by onsite engineering and the ultrasound machine will be checked for systems issues regularly. The machine is WiFi enabled and transmits all images after local storage to a central Syngo Cardiology ® Siemens image storage and reading processor. This is the standard imaging pathway at the University of Pennsylvania. Images can be read with analysis performed on a workstation as well. Images are stored locally. Images are stored on the CX50 machine for 30 days. All images are also uploaded at the end of the procedure to the patient’s chart.

6.2.2 Formulation, Appearance, Packaging, and Labeling

Over 2000 transesophageal echocardiograms are performed by the CV Anesthesiology group each year. The machine and probes in the ReTEECA trial are in the same family and cleaning paradigm as the general echocardiography probe group and are commercially available. No special cleaning procedures beyond the University of Pennsylvania standard will be performed.

6.2.3 Product Cleaning

On request, the TEE probe and package of enzyme cleaner will be brought in a disposable cardboard container to the patient's bedside by an anesthesiology technician during the rapid response or code call. After completion of TEE exam proceduralist will clean the probe with enzyme cleaner and places it in the box with "contamination side up." An ICU clerk or nursing assistant will then take container to inpatient processing (IP) in Ravdin/Dulles at the University of Pennsylvania. The probe will be "checked-in" by the perioperative technician and cleaned according to standard protocol.

6.2.4 Product Storage

After probe disinfection/testing procedure is complete, the probe is stored in a mobile aspects cabinet. The IP tech contacts ICU-nursing charge by calling the respiratory therapist to restock the device in its correct location. this is typically accomplished within 4-6hrs and follows standard hospital OSHA regulations for cleaning and handling of clinical devices. Then ICU clerk or nursing assistant goes to IP (OR) and retrieves the TEE probe/clean-container and transports it to the air sealed cabinet. A log of the leak testing and integrity electrical testing is kept as standard procedure.

6.2.5 Tracking

Perioperative technician will place specifically colored pendant on TEE probes to designate them as belonging to HVICU and which also serve as trackable markers by the Mobile Aspect cabinets. The device will also have a Radiance tag on TEE probes in order to track them throughout hospital. The radiance tag is a GPS geolocation tag to keep track of the location of the TEE probe. Radiance and Mobile Aspects tracking systems can be used to track probes, confirm inventory and track personnel who removed and replaced probes from Mobile Aspects cabinets – which is used for all devices at the University of Pennsylvania.

6.2.6 Chain of Custody

A chain of custody document will be kept and a monthly report of the device tracking the devices maintained.

6.3 Measures to Minimize Bias: Randomization and Blinding

There is no active recruitment for this study since it is not possible to actively and prospectively identify patients who will have in-hospital cardiac arrest. The subjects will be enrolled under exception from informed consent, 21 CFR 50.24.

Patients eligible for the study are those patients as listed in the inclusion and exclusion section of this protocol. Patients will be allocated by a month-to-month basis. This study has been designed to minimize bias by creating a separate RescueTEE team from the cardiac arrest treating team. Cardiac arrest can occur in many different locations in the hospital and the caring team is defined as the rapid response team or the ICU team based on the location of the cardiac arrest. The RescueTEE team is distinct and different from the team directing the cardiac arrest. This is in attempt to limit the bias that RescueTEE has on treating decisions. All other factors of the cardiac arrest will be standardized. Cardiac arrest protocol will follow the University of Pennsylvania Clinical emergencies Committee guidelines. The LUCAS device will be used to standardize chest compressions. Additionally, all defibrillators at the University of Pennsylvania are manufactured by Zoll Medical. These defibrillators have depth of chest compression pads with a gauge meter to standardize compression depth and force. This ensures high quality standard CPR between both arms of the study and further reduces bias. Both groups CPR quality is assumed to be exactly the same except the explanatory variable of image guidance. Code occurrences are managed and clinically coordinated by the rapid response team which ensures high quality code management and standardization. The code team will dictate

medication administration according to the AHA ACLS guidelines. Intra-arrest care and post cardiac arrest care will follow hospital guidelines which conform with national guidelines.

The randomization scheme is as follows: Conventional ACLS will be allowed to occur in a randomized sequence of months while image guided Rescue TEE will be performed on the alternating months where conventional ACLS was not performed. The RescueTEE will be performed at the point of care and at the time of cardiac arrest. If the cardiac arrest occurs outside of the ICU, the ICU team will be blinded to the randomization when the patient arrives to the ICU after the cardiac arrest. If the cardiac arrest occurs in the ICU the ICU team during the code will be not be blinded, however all efforts will be made to keep partial blinding as clinically appropriate. Breaking the blinding code can occur if the information from the RescueTEE is critical from a clinical standpoint and would constitute greater harm to the patient if withheld. Clinical decision making will be preferred to be driven by formal echocardiography, and recommendations by the RescueTEE care team will be to corroborate information with a formal sequence if clinically indicated; however, if RescueTEE information needs to be divulged then this will be done on a case-by-case basis. The PI and Co-PI will be immediately notified. Additionally, if any of the SAE events occur this will also be released to the care team providers.

We expect patients in both groups to similarly reflect diversity in gender, ethnic background, severity of illness, duration of cardiac arrest, and to receive the same therapy except one will have image guided Echo-ACLS with Rescue TEE while the other will have standard non-image guided ACLS.

After the code and imaging patients will be clinically followed with chart review and neurological evaluation. Endpoints of mRS score at the various time points listed in section 4.1 will be blinded. These will be acquired by a research team member by someone trained in neurological assessment and competent however blinded to the actual type of ACLS performed. This will be accomplished with chart review and via telephone interview or in-person interview if possible.

6.4 Study Intervention Compliance

The study will rely on the Rescue TEE team to maintain competence and compliance with record keeping. This is a pragmatic clinical trial comparing a well-established use of TEE during cardiac arrest. Standard of care will be used for ACLS and RescueTEE guidance will be administered by board certified or eligible echocardiographers. The PIs will monitor the delivery of the protocol and to which arm each patient is randomized to. If any deviation is detected this will be addressed by the study group immediately.

The study PI and Co-PI will be responsible for ensuring the ongoing quality and integrity of the research study. Independent monitors will be assigned to conduct routine data safety and quality monitoring procedures.

7 Study Intervention Discontinuation And Participant Discontinuation/withdrawal

7.1 Discontinuation of Study Intervention

Due to the short nature of exposure to the study intervention namely, RescueTEE during ACLS and the likelihood of a lack of LAR during the therapeutic window, rarely will patients be discontinued from the study intervention at the time of TEE. However, the physician MD who is performing the TEE may opt to discontinue the patient from the study during RescueTEE ACLS due to a SAE or AE or other clinical contraindication in a pragmatic fashion. However, discontinuation from RescueTEE does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes

from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed.

The data to be collected at the time of study intervention discontinuation will include the following:

- Adverse events
- Significant adverse events
- Care rendered due to SAE or AE

Discontinuation of life-sustaining efforts in either study arm will be based on the expressed wishes of the patient, LAR, or family in consultation with the treating MD physician.

7.2 Participant Discontinuation/Withdrawal from the Study

Participants are free to withdraw from participation in the study at any time upon request.

An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best clinical interest of the participant
- Disease progression which requires discontinuation of the study intervention
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

Educational material and consent for continued participation will be performed with the LAR or patient as appropriate after each patient is enrolled. After the conclusion of the study data will be entered into a Redcap database and disclosure will be completed with the LAR or patient.

As per EFIC Protocol: If a LAR or family member arrives and objects to the subject being in the study (verbal objection is acceptable), then treatment is discontinued, but the data up to that point remains in the study. If no LAR is available, then the subject remains enrolled in this EFIC study until the subject or family/LAR withdraws the subject from the study (if applicable). The reason for participant discontinuation or withdrawal from the study will be recorded. Discontinuation or withdrawal of a subject may also occur because of study closure due to DSMB review.

Consent for continued participation in the ReTEECA trial will be obtained. Furthermore, family members will be educated on the enrollment into the trial as per the EFIC standards and outlined in the EFIC documentation. After the initial RescueTEE no further invasive interventions will be performed. Chart review will be conducted as well as neurological screening and interviews during follow up. (See EFIC)

Data that is collected from patients prior to withdrawal will remain in the study. If a study subject, after enrollment, decides to no longer participate in the study, the initial data is required by the FDA to remain in the study for analysis. (See EFIC for details)

7.3 Lost to Follow-Up

The ReTEECA Trial allows for up to 15% loss to follow-up in its sample size calculation. Every effort will be made to keep such losses to a minimum. In general, occurrences of serious adverse effects which require terminating exposure to the investigational device or procedure will be counted as treatment failures.

A participant will be considered lost to follow-up if he or she fails RescueTEE, is unable to be found for mRS follow up, or for survival follow up, or is unable to be contacted by the study site staff.

The following actions must be taken if a participant cannot be contacted for follow up screening or is unable to be located for survival data.

- The study coordinators will attempt to contact the participant and reschedule the missed follow up neurological assessment over 2 weeks and counsel the participant on the importance of maintaining the assigned evaluation and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts will be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 Study Assessments And Procedures

8.1 Efficacy Assessments

8.1.1 Rescue Transesophageal Echocardiography

A transesophageal echocardiogram, or RescueTEE is an alternative way to perform an echocardiogram. A specialized probe containing an ultrasound transducer at its tip is passed into the patient's esophagus. Although TEE is considered an invasive procedure a single-center study with 10,000 TEE demonstrates that TEE examinations are associated with a very low risk of esophagogastric trauma when performed in a safe setting by experienced operators.³⁰ In particular, in 10,000 TEEs the study found one case of hypopharyngeal perforation, two cases of cervical esophageal perforation, and no cases of gastric perforation.^{30,37} During CPR while a patient is either pulseless or in a ventricular rhythm the primary purpose of the medical team is to revive life and restore cardiopulmonary function. Therefore, the POC RescueTEE in our study is deemed as an emergency procedure and we are evaluating if this can help lead to less mortality and improved code outcomes.

See attached PowerPoint presentations and videos for basic knowledge regarding RescueTEE. This lecture series was created and delivered to physician fellows and attending staff in order to educate board certified and board eligible MDs in the process for RescueTEE. RescueTEE is a subsection of specialized knowledge and application under the umbrella of TEE. RescueTEE is when a TEE is performed in a situation of clinical duress such as ACLS and CPR. Although these lecture series do not supplant clinical expertise, they are intended to create a standardized knowledge base for the RescueTEE MD when in a IHCA situation. This will allow for reduction in bias for the study. Furthermore, as standard definitions dictionary has been created for the common diagnoses and pathologies found during RescueTEE. This dictionary will provide the RescueTEE MD with a standard language for accuracy and precision when making a diagnosis during ACLS for the code leader MD. For example, to diagnose a pulmonary embolism as the case of IHCA we went through the following process. First education regarding the use of RescueTEE to diagnose pulmonary embolism was completed. Subsequently the definition for accurate diagnosis of PE was defined as an echogenic mass found in the venous system, RA, RV or pulmonary artery causing hemodynamic and echocardiographic evidence of heart failure and arrest. Finally, precision for the diagnosis of PE was defined based on the location and degree of obstruction as well as the ability to see a PE resolution upon administration of tPA therapy or institution of VA ECMO in

cardiac arrest. Similar education and accuracy/precision was done for other several diagnoses possible through RescueTEE.

See Attachments – Education PowerPoints

8.1.2 Neurological assessment

The Modified Rankin Scale Score (mRS) will be assessed by mRS-certified research personnel blinded to study subject randomized group assignment. The mRS will be assessed by telephone or in-person interview at hospital discharge, 3 and 6 months. See section 6.3 for a description of the methods of accomplishing blinded assessments.

Criteria for choosing an instrument to measure neurological status include prior data about reliability and validity, availability of instruments suitable for a multicenter trial, and application to prior cardiac arrest survivors. The Modified Rankin Scale (MRS) has face validity and can be determined in person or over the telephone. mRS has concurrent validity with other measures of neurological recovery after stroke and brain injury.^{38,39} Use of a structured interview in a recent study of stroke patients improved the weighted kappa from 0.71 to 0.91.⁴⁰ The only previous published applications of mRS to survivors of cardiac arrest evaluated a cohort of neurosurgical patients with in-hospital cardiac arrest and a cohort of survivors of out-of-hospital cardiac arrest.^{41,42}

8.2 Safety and Other Assessments

A transesophageal echocardiogram, or TEE is an alternative way to perform an echocardiogram. A specialized probe containing an ultrasound transducer at its tip is passed into the patient's esophagus. Although TEE is considered an invasive procedure a single-center study with 10,000 TEE demonstrates that TEE examinations are associated with a very low risk of esophagogastric trauma when performed in a safe setting by experienced operators.³⁰ In particular, in 10,000 TEEs the study found one case of hypopharyngeal perforation, two cases of cervical esophageal perforation, and no cases of gastric perforation.^{30,37} During CPR while a patient is either pulseless or in a ventricular rhythm the primary purpose of the medical team is to revive life and restore cardiopulmonary function. Therefore, the POCUS TEE in our study is deemed as an emergency procedure and we are evaluating if this can help lead to less mortality, better survival, and improved code outcomes.

The exclusion criteria for the study include patients who are not intubated, those with on-going aspiration, airway injury, esophagectomy, active upper GI bleeding, ongoing hemoptysis, or pregnancy.

The determination for these factors will be based on clinical exam at the bedside during assessment for RescueTEE by the RescueTEE MD. Due to the short and limited therapeutic window time and the critical time between cardiac arrest and RescueTEE placement there may be inadvertent TEE placement in patients that should have been excluded. This also includes patients who are DNR/DNI. Typically, the code team at the location will be queried to ascertain the code status however, screening failure may occur.

If screening failures occur then the study PIs will be notified and patient participation will be terminated upon realization of screening failure; however, the data collected until that point will remain in the study as per the FDA guidelines.

Following the cardiac arrest, data will be collected from the standardized code sheet that is completed from every code in the hospital. This data includes the following:

- Vital signs (e.g., temperature, pulse, respirations, blood pressure).

- Electrocardiograms (ECGs): rhythm before, during and after cardiac arrest as well as any changes in relation to RescueTEE findings or interventions intra-arrest.
- Radiographic or other imaging assessments. Follow up TTE or TEE as clinically indicated. Follow up CT scanning will be done if there is a clinical suspicion of esophageal injury.
- Administration of questionnaires or other assessment including mRS screening

Children, pregnant women, fetuses, neonates, or prisoners are not included in this research study. See EFIC Study protocol.

8.3 Adverse Events and Serious Adverse Events

ACLS management

Code simulation will be done prior to the start of the study to familiarize the code team with regards to the actual methodology and expected information from the RescueTEE team. Scripted dialog will also be made to ensure that specific parameters of conversation are kept. The TEE team will be positioned contralateral to the respiratory therapists to mitigate interference with ventilation and airway during ACLS.

A formal education session with the nurse managers for the code team and the medicine residents will be done at medicine grand rounds. Formal grand rounds will also be given to the anesthesiology airway team. The study was evaluated at the clinical emergencies committee and ongoing project improvement will be independently implemented. Time from code call to TEE placement will be recorded. Events during the TEE regarding interference with ACLS, CPR or code management will also be recorded in the CRF. This information will be directly provided to the study PIs and coded as MAE/SAEs. Revisions to study modifications will be made if any interference is found to standard ACLS. At no time will ACLS be halted or interfered with for RescueTEE probe placement. It is assumed that ACLS and CPR in both arms are identical.

TEE Probe Safety to patient

Retrospective review will be used to determine if esophgodigestive or thermal injury occurred for those patients who survived and are able to participate in clinical evaluation of these types of injuries. This is included as standard follow up as part of the chart review from the ReTEECA trial. Furthermore, for any patient who dies from IHCA and has an autopsy report, we will review the report for esophgodigestive or thermal injuries if a RescueTEE was performed.

A data safety monitoring committee (DSMB) consisting of three internal University of Pennsylvania staff, independent of the study will be used as a monitor for SAE/MAEs. Of note, the X8-2t probes have been in use since the 1990s and are commercially available. There are two area of engineering that are important to address for the ReTEECA trial. First is the ability of the patient to tolerate a TEE probe during chest compressions and second the probe to withstand the forces of CPR and normal esophageal pressures during ACLS. Most of the literature on the safety of TEE was completed in the 1990s. A seminal paper in the 1990s has demonstrated that minimal esophageal injury occurs with prolonged indwelling TEE use. The group studied an animal model and had a TEE scope duration of 4.6 hours. After excising the esophagus, they found no injuries, both mucosal or thermal.⁴³

Based on this data cardiac anesthesiologists over the past forty years routinely use TEE during cardiac surgery for greater than six hours in hospitals throughout the country. Second a separate study was completed in animals to determine whether the pressure produced by contact between a TEE probe and the esophagus was sufficient to cause esophageal damage. The pressure in the esophagus was measured at 4, 6, 8, and 12 hours and at probe placement

and they found that with maximum probe ante flexion and retro flexion the average pressure in the esophagus was 17 mmHg. One animal did have pressures up to 60 mmHg however there was no evidence of injury.²⁶

Although this data has been done on patients not undergoing CPR, as mentioned in Table 1, several observational studies have been completed in the recent past with patients undergoing CPR and with a TEE probe in place. No injuries have been reported. The evidence that the TEE probe is unlikely to injure the esophagus during CPR is based on the predominating intrathoracic pump theory of CPR, in which the esophagus sees pressures of 30-60 mmHg during chest compressions. This is based on the animal work in the 1980s where a balloon tipped catheter was placed in the esophagus of 15 dogs during chest compressions.²⁵ Since this publication several thousands of patients have had chest compressions with a TEE probe in place, in particular in cardiac surgery operating rooms and in cardiology catheterization labs on a daily basis. We have attached several case image-videos of a patient undergoing CPR with a TEE probe in place.

TEE probe safety to TEE machinery

TEE probes are reprocessed centrally by an automatic scope reprocessor machine at HUP. Based on the automated scope reprocessor (AER) devices instruction for use (IFU) and the Healthcare Infection Control Practices Advisory Committee (HICPAC) division of the CDC, these devices have an intrinsic amount of generated pressure of water and sterilizing cleaning solution delivered to clean the TEE scope. This is usually set by monitoring the inflow and outflow pressure monitor. According to the operator manual of the Olympus ER-30 model, 1.85 ± 0.05 kgF/cm² of pressure is applied to the TEE probe and 17 Liter/min in inflow water is delivered. This translates to a 1325 mmHg cleaning force which is significantly higher than any force encountered during CPR. However, to monitor the effect of CPR and defibrillation on the integrity of the TEE standard scope processing measures will be used.

The leak test consists of a manual leak test and an automatic leak test in the AER. It is a very important step to protect the electronic endoscope and to ensure that the casing has not been compromised. No air bubbles should appear after the water-resistant cap is attached.

Standard Processing will include:

- Electrical leakage testing. This is a very important procedure that should be performed regularly, using appropriate testing equipment (sometimes supplied by the TEE probe manufacturer). Electrical leakage signifies a break in the integrity of the probe housing/insulation, which could potentially be harmful for the patient, and also could lead to leakage of fluids and subsequent damage to the interior of the TEE probe.

This step will ensure that defibrillation does not compromise the integrity of the scope.

- Regular visual inspection of the probe and shaft housing for breaks, bite marks, etc.
- Inspection and testing of the connector for bent pins, cracks, etc.
- Evaluation of the integrity of the connecting cable
- Regular testing of the probe's articulation mechanism (knobs on control handle)

All of these steps are current standards at HUP and a case log is generated for cleaning and analysis. We know from clinical use that very rarely do these devices fail tests. Similar to the earlier scenario of active CPR with TEE probes, we have ample clinical evidence that TEE probes can withstand defibrillation routinely because over 60% of cardiac surgery patients require defibrillation at the time of separation from cardiopulmonary bypass. Based on this information and the fact that TEE probes maintain their electrical integrity we suspect very little chance of TEE probe malfunction due to defibrillation.

8.3.1 Definition of Adverse Events (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

- Misdiagnosis without iatrogenic harm to the patient
- Therapeutic intervention based on misdiagnosis without iatrogenic harm to the patient
- ETT dislodgement during CPR
- Missed Diagnosis without harm to the patient
- Delay in CPR
- Interference with ACLS
- Thermal Injury from Defibrillation
- Minor airway bleeding or esophageal bleeding

8.3.2 Definition of Serious Adverse Events (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

- Misdiagnosis with direct harm to the patient
- Therapeutic intervention based on misdiagnosis with harm to the patient
- Missed Diagnosis with harm to the patient
- Esophageal Perforation/Tear requiring intervention
- Severe Airway or esophageal bleeding

We will use the University of Pennsylvania clinical trials and safety monitoring mechanism as an external auditor. We will also have internal MAE/SAE audits. The PI will make the determination regarding the AE to the study intervention. Aerodigestive and esophgodigestive injuries due to TEE probe placement during CPR will be captured in the CRF. Incorrect clinical management and or incorrect image interpretation will be assessed on a case-by-case scenario by the primary investigator and co-investigator.

8.3.3 Classification of an Adverse Event

8.3.3.1 Severity of Event

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning. Including altering medical plans

- **Severe** – Events interrupt a participant’s usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term “severe” does not necessarily equate to “serious”.

8.3.3.2 Relationship to Study INTERVENTION

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

The PI and Co-PI will monitor every TEE study performed and complete a post TEE safety evaluation form. This data will be stored and project improvement will be done at intervals of the 25th exam, 50th exam, 75th exam, and 100th exam. If there are adverse events, thereafter, they will be reported individually. In order to follow up on SAE and AE we will perform a chart review which includes evaluation of follow up CT scans and daily progress notes. Any mention of the defined AE and SAE will be encoded based on the pre-specified AE/SAE data dictionary.

- **Related** – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

8.3.3.3 Expectedness

The study PI and Co-PI will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.3.4 Time Period and Frequency for Event Assessment & Follow-Up

The occurrence of an AE or SAE may come to the attention of study personnel during resuscitation, hospitalization, study visits and interviews, or upon review by a study monitor. Information to be collected includes event description, time of onset, clinician’s assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event.

The PI or designated research staff will record all reportable events with start dates occurring any time after enrollment at the last day of study participation all adverse event will be marked as resolved or continued with or without sequelae. At each study follow up visit, the investigator will inquire about the occurrence of SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3.5 Adverse Event Reporting

The investigator will promptly notify the Penn IRB of all on-site unanticipated adverse events that are related to the research activity. Other unanticipated problems related to the research involving risk to subjects or others will also be reported promptly. Written reports will be filed using the HS-ERA and in accordance with the Penn IRB timeline of 10

working days. Pathology autopsy report will also be used if available. Independent safety monitoring committee will review the study on a biannual basis.

8.3.6 Serious Adverse Event Reporting

This very critically ill study population is recognized and expected to experience initial and repeated life-threatening events throughout resuscitation and hospitalization. Accordingly, following consultation with the Food and Drug Administration, investigators will not track or report adverse events, expected to be nearly continuous in all patients.

Serious adverse events will be tracked and reported as described below. Investigators will further track the frequency of serious adverse events, compare the study frequency with patients treated similarly previous to and outside the study, and report any significant increased frequency based on investigator clinical judgment and experience.

8.3.7 Reporting Events to Participants

All SAE and AE will be reported to the patient and clinical care team immediately from when the research team became aware of the event and corrective clinical management will be undertaken.

8.3.8 Reporting of Pregnancy

Pregnancy, although possible, is unlikely. In case pregnancy is identified after resuscitation and intervention, the OB/GYN teams will be contacted to consult and manage related issues.

8.4 Unanticipated Problems

8.4.1 Definition of Unanticipated Problems

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research (“possibly related” means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

This definition could include an unanticipated adverse device effect, any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3(s)).

8.4.2 Unanticipated Problem Reporting

All UADE will be reported to the sponsor-investigator within 72 hours from when the research team became aware of the event.

8.4.3 Reporting Unanticipated Problems to Participants

All UADE will be reported to the patient and clinical care team immediately from when the research team became aware of the event and corrective clinical management will be undertaken.

9 Statistical Considerations

9.1 Statistical Hypotheses

This study is a prospective observational study – Conventional ACLS versus RescueTEE image guided ACLS for IHCA. The study population is patients undergoing cardiac arrest. Data will be obtained and uploaded in to a central Redcap database. Study forms, code sheets, patient records and EMR data will be obtained in a retrospective fashion after the code event. The randomization scheme is as follows. Image guided ACLS will be performed on alternating months versus Conventional ACLS. The statistical design for the study is a Bayesian Adaptive Clinical Trial. This entails periodic evaluation of the primary outcomes in the two groups. At such evaluations the patients will be weighted towards the better of the two outcomes to allow for deviation from 1:1 sampling. This will allow for potential reduction to the interventional arm if the exposure demonstrates no difference from the conventional arm.

The first primary outcome will be percent survival to hospital discharge (Proportion). Therefore, the hypothesis mathematically is as follows:

Null Hypothesis: $H_0: p(\text{c-CPR}) = p(\text{i-CPR})$

Where H_0 is the null hypothesis

Where c-CPR = conventional CPR

Where i-CPR = image-echo CPR

$H_a: p(\text{c-CPR}) > p(\text{i-CPR})$

Where H_a is the alternative hypothesis

The threshold has been chosen to ensure type I error rate control at the nominal 0.05 level. The study sample size has been selected to provide 90% power for rejecting the null hypothesis under the targeted alternative scenario with $p(\text{c-CPR}) = 23.7\%$ versus $p(\text{i-CPR}) = 38.7\%$. The reported survival from IHCA is estimated at 23.7% based on literature.⁷ An effect size of 15% is clinically reasonable where the better survival is attributable to the intervention arm.

This will be a categorical variable. The second primary outcome regarding RescueTEE interventional and therapeutic guidance will also be a categorical variable. The final component of the primary outcome regarding survival to the end of the code, ICU survival, and neurologically intact mRS 0-3 hospital survival which will be recorded as binary (yes, no) and scored on the scale. There will be survival time data built as a Kaplan Meier survival curve. For survival time analysis the event of interest will be dead/alive (all-cause mortality) status at specified time points (code to -> End of Code, ICU discharge, 30 days post arrest, Hospital Discharge, 90 days post arrest). This data will then be compared as a fisher exact single-tail risk ratio compared to similar cardiac arrest survival for codes without TEE. This will be reported as percent survival and risk ratio.

9.2 Sample Size Determination

In order to calculate a sample size, we used Bayesian Assurance for two proportions with beta priors for $P(\text{i-CPR})$ at various different beta prior assumptions. We used the software tool nQuery® to model our sample size. We also used

nQuery® to model our adaptive Bayesian design. We used three different beta prior assumptions to ascertain an appropriate sample size:

1. Beta (0.5,0.5)
2. Beta (0.4,0.6)
3. Beta (0.6,0.4)
4. Beta (1,1)
5. Beta (35,57) – Optimistic Prior
6. Beta (35, 35) – Skeptical Prior
7. Beta (35, 47) – Clinically optimized prior based on evidence, expert opinion, and mildly favorable prior

As a reference sample sizing using a basic Chi-squared test for two proportions with a power of 90% the two group χ^2 test with a 5% one-sided significance level will have 90% power to detect the difference between group 1 proportion $p(c-cpr)$ of 0.237 and a group 2 proportion $p(e-CPR)$ of 0.387 (odds ratio of 2.032) when the sample size in each group would be 199.

For this study we are using standard sample size calculation based on the primary outcome of survival to hospital discharge and power estimation for an alpha level of 0.05 and power of 90%. Based on the American Heart Association statistics the discharge survival rate for adults experiencing IHCA is 23.9%.⁷ This does not account for neurological status which is our secondary outcome, and the study will not be powered for this outcome. We estimate to detect a 15% difference in survival to discharge. If, as a hypothetical, we have 250 RescueTEE guided ACLS for IHCA we will have expected 60 patients to survive to hospital discharge with conventional management and expected survival with RescueTEE with an increase of 15% to hospital discharge would result in 97 patients to survive until hospital discharge. This is an absolute difference of 37 patients. The most common diagnosis in cardiac arrest have clinically and historically been based on statistical estimation; as the most common causes of arrest – 5Hs and 5Ts – namely hypoxia, hypovolemia, acidosis, hyperkalemia, hypothermia, cardiac tamponade, acute myocardial infarction, pulmonary embolus, and thrombus. We suspect that in 250 patients we will be able to pick up an additional 37 patients in with these particular diagnoses and then result in early interventions for improved survival.

Bayesian Assurance for Sample Calculation:

Now using our Bayesian Assurance for two proportions with beta priors we find the following sample sizing: Assurance level was set at 90%.

When the sample size per group is Beta prior (1-7), a one-sided two – sample test for proportions will have assurance of 90.21% to detect superiority at the 0.05 significance level, assuming the proportion of respondents (survival) in the control group $p(c-CPR)$ is 0.237 and the proportion of respondents (survival) in the treatment group $p(i-CPR)$ follows a prior Beta distribution of Beta (1-7) as listed above

N-values:

1. 333
2. 411
3. 257
4. 553
5. 358

6. 84
7. 176

What this demonstrates is that for the skeptical beta prior the trial can be halted at a sample size of 84 per group if there is no difference or trend toward no difference with 90% confidence for those who have skeptical prior pre-trial opinion on the prospect of RescueTEE ACLS. On the other hand, for the optimist a trial would require a sample size of 358 per group with no difference to confirm with 90% assurance of the outcome effects for the null hypothesis. Using a 15% dropout rate, and a slightly positive clinically optimized beta prior we estimate using a Bayesian Assurance of 90% in clinical trial confidence of the results **we should collect approximately 257 patients per group with a moderately optimistic prior.**

Interim analysis will be carried out at 50, 100, and 150 per patient groups for early stopping of the trial. Using nQuery® for Adaptive design in clinical trial progress we modeled the study as an interim monitoring and unblinded sample size re-estimation for two proportions and group sequential test of two proportions. Again using an alpha of 0.05 and a group 1 (c-CPR) proportion of 0.237 and group 2 (i-CPR) of 0.387 and the odds ratio of 2.032. At these specified times given 4 looks (50, 100, 150, and 200) that are equally spaced running the experiment 1000 times and based on the Alpha spending function O'Brien-Fleming which has equal values approximately equal at each exit the cumulative chance of exist and odds ratio are as follows:

Sample Size total (1:1)	100	200	300	400	500
OR to reach to stop trial	- 4.87	- 3.357	- 2.69	- 2.29	- 2.03
Cumulative Exit Probability of trial	0.1%	14.98%	56.59%	84.347	95.2%

We do not intend to reassess and change the blinded sample sizing through the course of the trial. It will remain at 257 per group unless directed by the DSMB.

9.3 Populations for Analyses

Baseline and demographic characteristics will be collected retrospectively through chart review. The echocardiographer will collect an inpatient sticker and baseline variables will be stored in a secured database, called CTMS and PennVault. This will include age, gender, time of code, duration of code, probe insertion time, cause of code, service running code, and location of code. We will also collect and report last known vital signs prior to code as a retrospective chart review of the data. Last lab values will also be reported. The demographics will include reason for hospitalization, length of hospitalization prior to RescueTEE placement.

9.4 Statistical Analyses

9.4.1 General Approach

Data will be obtained and uploaded into a central Redcap database. The initial encounter and code information will be updated retrospectively from the code event and the echo images will be linked to the code events. The primary outcome will be described using ordinal descriptions. Univariate analysis will be performed with the use of Mann-Whitney U test for continuous variables and fisher's exact test for dichotomous variables. The primary outcome, as described above, will be binary. The demographics will be classically descriptive. Cases will be compared to expectant management of code situation in the same study time period.

9.4.2 Analysis of the Primary Efficacy Endpoint(s)

The analysis of the primary outcome will be percent survival to code completion, percent survival to ICU discharge, and percent survival to neurologically intact survival based on a mRS score of 0-3 at hospital discharge in groups with or without TEE. Additionally, a binary outcome of percent of cases where TEE was able to diagnose pathology will be reported.

We will also categorize the diagnosis and the interventions performed as part of our primary outcome. We will look at the various types of diagnoses and interventions which will be reported as bar charts and pie charts as percentages of total number.

As defined above, this study is a clinical comparative outcomes study. We have developed a plan to assess the accuracy and precision of RescueTEE during IHCA. In order to provide the most optimal environment to assess the accuracy and precision for RescueTEE we will only use a select group of board certified echocardiographers for POC image interpretation. Each of the prespecified diagnoses of concern will have an echocardiographic data dictionary with strict formal definitions. (See Attachment for diagnostic definitions). After the echocardiographer has completed the exam blinded independent intra- and inter-rater reliability will be done both for diagnosis and intervention. For example, if an anterior wall acute myocardial infarction is diagnosed and the intervention suggested is percutaneous balloon angioplasty (PTCA) and cardiac catheterization then this study will be reviewed offline by the same echocardiographer in a blinded fashion at a later date to ensure intra-rater reliability. This set of images will also be reviewed by an independent board certified echocardiographer for matching or discordant diagnosis and interventional plan to determine inter-rater reliability. This will be reported as a Bland-Altman plot. If discordance is found a third-party adjudicator will be used to arbitrate the diagnosis and the intervention. This mechanism will ensure high standards for diagnostic precision and accuracy for RescueTEE. We will use standard echocardiographic objective outcomes to define each pathology. Furthermore, after the completion of ACLS, the follow up care team will be blinded to which arm the patient was enrolled in, i.e. conventional ACLS or RescueTEE ACLS. Therefore, follow up care and survival analysis will be based on natural outcomes from the ICU and post ACLS care. We will also collect data on historical codes as a control population as well as the randomization scheme described above. In this particular study we will use “no interventional control” as opposed to placebo control.

In addition to the aforementioned plan, for the handling of the data for the clinical comparative outcomes study, we will also assess the accuracy and precision of the RescueTEE based on alternative imaging modalities. So, for example, in a particular case if all reviewers of the RescueTEE images diagnose an AMI and intervened with PTCA; however, the true diagnosis was found to be something else, this situation would be highly precise but with low accuracy. The diagnosis will be confirmed by the cardiac catheterization that patient will undergo after the diagnosis of AMI based on TEE. In order to delineate the precision of RescueTEE we will ascertain, for example, if the patient had an AMI which territory the AMI occurred in. So, for example, if the diagnosis was a left anterior descending (LAD) AMI, and the catheterization result was found to be right coronary artery (RCA) AMI; the Rescue TEE will be accurate for the diagnosis of AMI but not as precise to the granular level of vessel territory. Another example as provided in the diagnostic definitions would be a RescueTEE diagnosis of pulmonary embolism without the ability to precisely locate where the pulmonary embolism (PE) is. In this case the patient would go to the catheterization lab or CT scan for confirmation of the PE and if a PE is found the RescueTEE would be deemed accurate however not as precise as the angiography or CT scan. So, in these scenarios the CT scan or catheterization would be as accurate however much more precise than the RescueTEE. Regardless, our primary endpoint is based on accuracy and outcomes are defined as survival; even in the setting of low precision.

9.4.3 Analysis of the Secondary Endpoint(s)

As defined above, this study is a clinical comparative outcomes study. We have developed a plan to assess the accuracy and precision of RescueTEE during IHCA. In order to provide the most optimal environment to assess the accuracy and precision for RescueTEE we will only use a select group of board certified echocardiographers for POC image interpretation. Each of the prespecified diagnoses of concern will have an echocardiographic data dictionary with strict formal definitions. (See Attachment for diagnostic definitions). After the echocardiographer has completed the exam blinded independent intra- and inter-rater reliability will be done both for diagnosis and intervention. For example, if an anterior wall acute myocardial infarction is diagnosed and the intervention suggested is percutaneous balloon angioplasty (PTCA) and cardiac catheterization then this study will be reviewed offline by the same echocardiographer in a blinded fashion at a later date to ensure intra-rater reliability. This set of images will also be reviewed by an independent board certified echocardiographer for matching or discordant diagnosis and interventional plan to determine inter-rater reliability. This will be reported as a Bland-Altman plot. If discordance is found a third-party adjudicator will be used to arbitrate the diagnosis and the intervention. This mechanism will ensure high standards for diagnostic precision and accuracy for RescueTEE. We will use standard echocardiographic objective outcomes to define each pathology. Furthermore, after the completion of ACLS, the follow up care team will be blinded to which arm the patient was enrolled in, i.e. conventional ACLS or RescueTEE ACLS. Therefore, follow up care and survival analysis will be based on natural outcomes from the ICU and post ACLS care. We will also collect data on historical codes as a control population as well as the randomization scheme described above. In this particular study we will use “no interventional control” as opposed to placebo control.

In addition to the aforementioned plan, for the handling of the data for the clinical comparative outcomes study, we will also assess the accuracy and precision of the RescueTEE based on alternative imaging modalities. So, for example, in a particular case if all reviewers of the RescueTEE images diagnose an AMI and intervened with PTCA; however, the true diagnosis was found to be something else, this situation would be highly precise but with low accuracy. The diagnosis will be confirmed by the cardiac catheterization that patient will undergo after the diagnosis of AMI based on TEE. In order to delineate the precision of RescueTEE we will ascertain, for example, if the patient had an AMI which territory the AMI occurred in. So, for example, if the diagnosis was a left anterior descending (LAD) AMI, and the catheterization result was found to be right coronary artery (RCA) AMI; the Rescue TEE will be accurate for the diagnosis of AMI but not as precise to the granular level of vessel territory. Another example as provided in the diagnostic definitions would be a RescueTEE diagnosis of pulmonary embolism without the ability to precisely locate where the pulmonary embolism (PE) is. In this case the patient would go to the catheterization lab or CT scan for confirmation of the PE and if a PE is found the RescueTEE would be deemed accurate however not as precise as the angiography or CT scan. So, in these scenarios the CT scan or catheterization would be as accurate however much more precise than the RescueTEE. Regardless, our primary endpoint is based on accuracy and outcomes are defined as survival; even in the setting of low precision.

9.4.4 Safety Analyses

The incidence of AEs will be recorded for all patients in the safety population and presented by treatment arm to the DSMB for review during the study, as well as summarized and compared across treatment arms in the final report of study results. AEs attributable to echocardiography will be reported separately. The statistical significance of differences in safety signal incidence between the 2 treatment groups will be reported. Emphasis will be placed on the presentation of primary study results, with statistical tests provided for guidance on the precision of estimates as indicated. The DSMB must weigh risks against benefits. Thus, interim presentations to the DSMB will include between-group comparisons of the relation of severe adverse events (including deaths) to favorable outcomes. Similar considerations apply to publication of study results when the trial is completed. The specific adverse events listed that

potentially reflect the safety of the image guided ACLS may or may not affect survival to hospital discharge or longer-term functional outcome

9.4.5 Baseline Descriptive Statistics

Baseline descriptive statistics in the two groups include the follow

Age

Gender

Race/Ethnicity

Location of Arrest

Witnessed

Code call time

Time at TEE placement (in i-CPR) Group

Time of ROSC

CPR duration

Resuscitation therapies administered

Airway placement

Medications administered

Interventions completed

ECMO initiation

tPA initiation

Cath lab activation

OR activation

Time of death

Initial labs (ABG, CBC, CMP, Coagulation profile)

First TTE or TEE formally obtained

Copy of code sheet from Media

9.4.6 Planned Interim Analyses

An independent DSMB will be appointed in order to ensure the safety of the subjects by monitoring adverse outcomes throughout the trial and by reviewing outcome data for both efficacy and possible harm. At least one bioethicist will be included in the DSMB membership. In addition, the Board will review the results of interim analyses. The DSMB must

review and approve the protocol before the study can commence. The DSMB will evaluate the rate of adverse events between the treatment and control arms at 6-month intervals. As noted above, the DSMB will be notified whenever the randomization allocation ratio is changed. The DSMB will be required to conduct a formal vote on a recommendation to stop the study if the posterior probability that one group is superior to the other exceeds 0.986. The DSMB will also monitor secondary study outcomes success rates between the treatment and control groups, and rates of adverse events. Per agreement with the FDA the study group will provide quarterly reports regarding survival and neurological outcomes (at discharge, 3 months and 6 months as data are available), so that direct patient safety (i.e., survival with good neurological trends) between the two arms can more closely be monitored. Meeting minutes will be kept following all DSMB meetings, where patient safety will also be evaluated. This log will be submitted to the FDA quarterly.

9.4.7 Sub-Group Analyses

The subgroup analysis will include the following analysis:

Echo-guided Extracorporeal CPR versus conventional CPR with extracorporeal life support

Early versus late catheterization lab intervention for acute myocardial infarction by echocardiography versus no echocardiography

male versus female

Age < 55 versus > 55

High versus low mRS score 0-3 versus > 4

These are exploratory analysis and the sample sizes are much smaller than the primary outcome. Therefore, the study is not powered for these endpoints but will allow for building future areas of interest and questions.

9.4.8 Tabulation of Individual participant Data

Patients in this trial will have complex clinical courses prior to hospital discharge. They will experience a wide variety of adverse events, many of them serious, some of them known complications of cardiac arrest and prolonged ICU stay. The Statistical and Data Coordinating Center (CTMS and Study PIs) will maintain detailed histories, by hospital course day, of adverse events and treatments. Tables comprised of such detailed histories will be available for examination by members of the DSMB. DSMB summary tables will classify the nature and frequency of adverse events essentially by collapsing such histories across treatment groups and other strata of interest. Neurological outcomes between the two arms will be closely monitored and quarterly reports will be created and submitted to the FDA.

9.4.9 Exploratory Analyses

In addition to the primary and secondary analyses described above, the SDCC will carry out non-pre-specified analyses in certain subgroups. This will include time of day of the event, laboratory findings, and treatments administered during the hospital stay. Such analyses may be carried out on emergent factors which were not anticipated or described at the beginning of the trial. As such, any hypothesis testing (p-values) arising from such analyses must be regarded as exploratory. They will need to be noted and reported to the DSMB and in publications emanating from the trial, but they will also need to be confirmed by future studies and will be clearly described as exploratory.

10 Supporting Documentation And Operational Considerations

10.1 Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Informed Consent Process

Due to the nature of this study – conducted at the time of cardiac arrest - we will request a waiver or alteration of required elements of consent with 21 CFR 50.24, Exception from Informed Consent (EFIC) Requirements in Certain Emergency Research.

The study will use Exception from Informed Consent (EFIC). See the EFIC Protocol enclosed.

Consent groups:

Patients will be randomized into one of two groups:

Conventional ACLS (c-CPR)

Image guided ACLS (i-CPR)

The c-CPR group will initially be enrolled under the waiver of informed consent (WIC). These patients will receive standard of care including ACLS, CPR, and high-quality chest compressions and will not be exposed to greater than minimal risk interventions. Once an LAR is present or the patient is re-capacitated, consent for continued participation will be sought. Patients who survive will have chart review as well as neurological mRS screening performed according to the schedule described in the methods section. If the patient dies intra-arrest, no consent for continued participation will be sought because only intra-arrest data will be collected.

For the i-CPR group, the research cannot be practicably carried out without EFIC. Subjects will be provided with additional pertinent information after participation if they survive the code event and have neurological and psychological capacity for communication. We will pursue a EFIC section 21 CFR 50.24 from the IRB. The proposed research is on human subjects in a life-threatening situation. Patients will be enrolled after overhead cardiac code calls are placed throughout the hospital. The therapeutic window is 10 minutes and therefore obtaining consent from the LAR is impractical and not feasible.

Obtaining consent is not practical or feasible during cardiac arrest. Second, it is impractical to prospectively identify patients who will have an IHCA. Thus, it would be extremely challenging to consent every patient in the hospital who may experience in-hospital cardiac arrest and therefore participate in the study. If, however, at the time of cardiac arrest there are family members available to consent during the therapeutic window, consent will be obtained verbally and RescueTEE imaging completed. If, however there is no immediate family members available at the bedside during the code situation, efforts will be made immediately after the code to explain the risks and benefits of the RescueTEE study and consent for continued participation will be obtained. Furthermore, if family is not reachable directly or via the phone post-cardiac arrest, then a second attempt at contacting the family and updating them will be done at the time of admission to the ICU. Ongoing attempts at obtaining consent for continued participation will be done by the study team. Patient readable material will be given to the family after the use of RescueTEE and placed in the patient chart. Finally, in the event of the patient regaining consciousness, consent for continued participation directly from the patient will be performed by the study team. (See EFIC for details)

In the setting of an emergency situation, where the survival to neurologically intact discharge after in-hospital cardiac arrest is ~15-20%, and immediate mortality is greater than 50%. We submit that the benefits of lifesaving diagnosis outweigh the low risk of injury from intervention. In order to provide process review and quality assurance we have

elected to provide independent oversight of this project to the University of Pennsylvania Code Committee. This committee comprising of over 40 members meets every month and discusses and reviews code events in the hospital. There are representatives from several disciplines including emergency medicine, internal medicine, advance practice nurses, etc.

Technical note

A verbal consent for refusal of participation mechanism has also been added to the study consent process. Verbal consent refusal is a mechanism, in the rare circumstance that a LAR or family member is immediately available at the bedside and also within the therapeutic window of 10 minutes when the RescueTEE team arrives. Practically speaking, most family members/LARs are ushered away from the bedside during a IHCA but this mechanism was added should the previously mentioned scenario arise. LARs consented with the verbal mechanism will be educated about the study with the option for refusal for consent verbally, or with the long form consent. This verbal mechanism is an avenue for an LAR to object to the patient's enrollment during IHCA if they so choose.

Summary:

The process is the following:

LAR at code – Can provide Verbal Refusal to participate

(Rare) LAR at code and consent is ethically possible – Traditional Consent Long Form

LAR after code – Conventional CPR – Waiver of Informed Consent for chart review and mRS screening

LAR after code – Intervention Echo-CPR – EFIC 21 CFR 50.24 for chart review and mRS screening

When patient regains capacity – re-consent patient directly for either arm for continued participation.

10.1.1.1 Consent/assent and Other Informational Documents Provided to participants

A procedure for prospective informed consent has been developed as is required by the regulations, in the unlikely event that a LAR can be identified within the therapeutic time window for the intervention and is able to provide a meaningful prospective surrogate consent for patient enrollment. However, it will not likely be possible in the ReTEECA trial for the reasons summarized in the scientific protocol, to delay treatment for most of the eligible patients long enough to identify and contact either a LAR or other family members. In circumstances in which it is impossible to identify a LAR within the therapeutic time frame, EFIC will be applied for the interventional group and waiver of consent for the conventional arm.

Prior to enrolling an eligible patient into the proposed trial with EFIC Waiver, the physician will see if the eligible patient has refused study participation by checking if the patient is wearing an opt-out bracelet with the phrase "ReTEECA declined." If the words "ReTEECA declined" are listed on the bracelet or known to the patient care team or code team, the patient will not be enrolled in the clinical investigation. If no "opt out" is identified, the patient will be entered into the study.

Subjects who are enrolled in ReTEECA trial with EFIC Waiver, or their LAR/family, will be informed of the subject's inclusion in the clinical investigation at the earliest possible opportunity. This will be done in person, after the patient is coherent and informed consent can be obtained as medically determined. An on-call study team member will speak

with the senior clinician to determine the stability of the subject and the appropriate time for speaking with the subject, or if not alert or capable of making informed decisions, a LAR or family member. The study team member will approach the subject (or LAR/family) to notify the subject or LAR/family about the subject's enrollment under EFIC or WIC, provide information about the study, about the subject's rights, the responsibilities of the investigators, and answer any questions about the study. At that time, the patient or the LAR will be asked to provide consent for continued participation in the study. A verbal objection to the study is acceptable. A written informed consent document will be used to document the subject's (or LAR/family's) decision to either continue in the study or to not participate any further. A copy of this form will be provided to the subject and another copy will be placed in the research record. Subjects who do not wish to continue to participate will be excluded from all further aspects of the study except for the use of data required by the federal agencies and permitted by the IRB to determine safety and efficacy. All data must remain in the study until such time as the subject or family/LAR decides to object to further participation in the study (i.e., withdrawal from the study). No further treatment is provided, and no further data is collected, however, all data up to the point of withdrawal remains in the study per FDA policy.

10.1.1.2 Consent Procedures and Documentation

Informed consent

is a process that is initiated prior to the participant or the individual's legally authorized representative agreeing to continue to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of continued participation will be provided to the participants and their families along with a description of what has occurred so far given initial enrollment under EFIC. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to continue to participate in this study

10.1.2 Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency, the Investigational Device Exemption (IDE) sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping

- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or Food and Drug Administration (FDA).]

10.1.3 Confidentiality and Privacy

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover imaging acquisition as well as to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor-investigator.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the University of Pennsylvania CTMS as well as Penn Redcap. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by University of Pennsylvania research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the University of Pennsylvania CTMS as well as Penn Redcap.

10.1.4 Future Use of Stored Specimens and Data

Patient information will be de-identified by software-based imaging techniques when imaging is analyzed. This encryption tool is available in all imaging-based storage systems. Imaging will be erased 5 years after the end of the study period. All data are anonymized, with records indexed by alphanumeric IDs; no names, SSNs, hospital record numbers, phone numbers, addresses or other identifiers will be stored.

Clinical data from patients will also be stored for the 5 years following the study conclusion. This includes code data, echocardiography reports, follow up data and survival data. This will all be stored electronically.

10.1.5 Key Roles and Study Governance

Principal Investigator

Jacob Gutsche MD

Associate Professor

Department of Anesthesiology and Critical Care

Asad Usman MD, MPH

Instructor

Department of Anesthesiology and Critical Care

Co-investigators

Justin Clapp PhD, MPH

Assistant Professor

Department of Anesthesiology and Critical Care, Anthropology

Benjamin Abella MD, MPhil

Professor

Department of Emergency Medicine

Cameron Baston MD

Associate Professor

Department of Pulmonary Medicine and Critical Care

Research Coordinators

Samantha Stein (PhD *in process*)

Department of Anesthesiology

Nathan Sands, BA

Emergency Medicine

Alikesei Basataski, MA

Department of Anesthesiology and Critical Care

DSMB

Scot Falk, MD

Department of Anesthesiology and Critical Care

Kristen Welsh, NP

10.1.6 Safety Oversight

Safety oversight will be under the direction of a Data and Safety Monitoring Board (DSMB) composed of individuals with the appropriate expertise, including Head of the clinical emergencies committee and Kristen Welsh NP. Members of the DSMB should be independent from the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest. The DSMB will meet at least semiannually to assess safety and efficacy data on each arm of the study.

The ReTEECA data safety monitoring process is intended to review the events surrounding the code, the ability or inability to place TEE probes, patient safety, and image quality for every one in ten RescueTEE – randomized patients enrolled in the trial. This will include image review, image quality, ability to obtain all rescue views intended, review the events of the code, and review the probe placement attempts. This is not intended to address autonomy of the patient but the actual safety and monitoring of data and data acquisition. If there are concerns with regards to the RescueTEE ReTEECA trial and the collaboration with the hospital code teams the study will be halted until further review.

There will be a team of three reviewers for the safety monitoring of the study from outside the Department of Anesthesiology and Critical Care who will provide independent review alongside the clinical emergencies committee at HUP which is a team of 40 staff members independent to the study. We will use the office of clinical research to ensure that this is an independent process and also report biannually our progress to the clinical emergencies committee which oversees safety during all rapid responses and codes in the hospital. We will utilize the support from the Department of Medicine, Pulmonary and Critical Care and from the Department of Emergency Medicine for this task. In addition to this, Kelly Hoesnich RN, the nurse supervisor for the CTICU founder 5 will be a point person ensuring that TEE probes are housed in a sterile environment, cleaned after each exam and sterilized appropriately. A TEE probe cleaning mechanism has been approved by the clinical processing division (CPD) department at the University of Pennsylvania and will be housed in a sterile cabinet provided by the respiratory therapy (RT) department in the CTICU.

In addition to data monitoring and collection review the two PIs of the study will review and provide continuous process improvement in study processes. If any items are found that need to be updated, the IRB will be notified immediately.

10.1.7 Clinical Monitoring

The study PI and Co-PI will be responsible for ensuring the ongoing quality and integrity of the research study. Independent monitors will be assigned to conduct routine data safety and quality monitoring procedures.

The sponsor-investigator Dr. Usman and Dr. Gutsche will permit direct access for the study monitors and appropriate regulatory authorities to the study data and to the corresponding source data and documents to verify the accuracy of these data. Independent monitoring of the clinical study for clinical protocol and IDE application compliance will be conducted by University of Pennsylvania pre-identified data safety monitoring board (DSMB)

Our local DSMB will confirm that study activities are in compliance with the approved protocol and applicable regulatory authorities (FDA, IRB, local and State regulations).

The DSMB as well as the clinical emergencies committee will include Anesthesiology Associate professor and head of the Clinical Emergencies Committee (CEC) and nurse practitioner Kristen Welsh NP as well as code team nurse practitioner Stacie Neechie NP. They will review and adjudicate serious and unexpected adverse events independently from the PI and co investigators.

Frequency of safety checks will occur:

- After IRB approval
- As soon as possible after the first subject is enrolled
- During the study data collection phase
- After the last subject has completed his/her participation in the study

This monitoring schedule may be revised based on the following considerations:

- Accrual rate
- Protocol deviations or non-compliance with regulatory authorities
- Magnitude of data corrections required
- Study stage (e.g. start-up or follow-up)
- Complexity of the trial
- Request (IRB, Investigator, other etc.)
- DSMB recommendation

The DSMB will evaluate the study quarterly, at a minimum, in a targeted on-site fashion. The sponsor-investigator will permit direct access to the study monitors and appropriate regulatory authorities to the study data and to the corresponding source data and documents to verify the accuracy of these data.

Primary responsibilities of the monitors will include verifying the following:

- Investigator qualifications
- Facilities and equipment
- Storage, dispensing and disposition of investigational products
- Protocol compliance
- Informed consent
- Training and delegation of authority
- Subject eligibility
- Recruitment, screening and enrollment
- Verification of data and data clarification
- Adverse event reporting
- FDA correspondence – Provided quarterly as minutes
- Deviations

10.1.8 Quality Assurance and Quality Control

This study will be performed at a single center. We will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution. In this particular study we will run quality control metrics on the Redcap data form to ensure timely entry of code data, echocardiographic data and imaging upload. Data entry beyond 14 days will be noted and reported to the study PI.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and neurological screening scores are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonization Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities. The study PI and co investigators will screen data for quality control and quality assurance. Key areas include timely and accurate data entry in echocardiography reports, timely and accurate data entry for code sheets from the medical record, and timely and accurate follow up data for survival. This granular data will be collected and maintained by the research coordinators of the study.

10.1.9 Data Handling and Record Keeping

10.1.9.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

The investigator-sponsor will maintain records in accordance with Good Clinical Practice guidelines; to include:

- FDA correspondence related to the IDE application and investigational plan; including copies of submitted Form FDA 3500 A, supplemental IDE applications, current investigator lists, progress reports, notice of device recall or disposition, and failure to obtain informed consent reports;
- IRB correspondence (including approval notifications) related to the clinical protocol; including copies of adverse event reports and annual or interim reports;
- Current and past versions of the IRB-approved clinical protocol and corresponding IRB-approved consent form(s)
- Signed Investigator's Agreements and Certifications of Financial Interests of Clinical Investigators;
- Curriculum vitae (investigator-sponsor and clinical protocol sub-investigators);
- Certificates of required training (e.g., human subject protections, Good Clinical Practice, etc.) for investigator-sponsor and listed sub-investigators;
- Normal value(s)/range(s) for medical/laboratory/technical procedures or tests included in the clinical protocol;

- Instructions for on-site preparation and handling of the investigational device and/or study treatment or diagnostic product(s), and other study-related materials (i.e., if not addressed in the clinical protocol);
- Decoding procedures for blinding of month
- Consent forms
- Code sheets
- Subject enrollments
- EFIC documentation and data analysis
- Public disclosure forms
- Interim results
- Follow up forms
- Audio files

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into Penn Redcap, a 21 CFR Part 11-compliant data capture system provided by the PennVault and PennCTMS as well as Penn EPIC integrated Redcap. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

Data analyses will be carried out using SAS (version 9.3 or later), Stata (version 11 or higher), Microsoft Excel (2021) or R (version 3.2 or later).

All data files are backed up to a remote location on a daily basis, and can be restored by designated data management personnel in case of system failures or power outages. Access to our system by unauthorized entities is closely monitored. The RedCap system automatically includes a data dictionary and complete specifications with regard to data type (e.g., numeric, character, dates, ICD-10 codes, other).

Data will be collected through Penn Redcap forms. Data will also be uploaded to a secure site that is maintained by the University of Pennsylvania called the clinical trials management software (CTMS) and the PennVault. The PennVault is a location where secure documents can be stored. External and internal audit mechanisms are built in to allow for reviewers to check the progress of the study and monitor SAE and AE. All IHCA codes at HUP have a nurse documenting on a live code sheet. This sheet is subsequently uploaded into the EPIC chart. The RescueTEE report will be completed by the clinician performing the examination and then will be transferred over after the event. A master list containing PHI and subject ID numbers separate from any data forms, electronically. This account will be restricted to IRB approved researchers only.

Other forms that will be collected in the Redcap will be regarding survival information, demographic information, and also if "Visit 1" which refers to follow up formal TEE/TTE if completed in the ICU for those patients surviving the initial cardiac arrest. Direct responsibility for IDE documentation and handling will be done by Alieksei Basatiski research coordinator in the Department of Anesthesiology, as well as the clinical research coordinator for the trial Samantha

Stein. Ultimately, all records will be held through the study investigator-sponsors Dr. Asad Usman and Dr. Jacob Gutsche.

Study participation will be documented in plain generic terms through a statement that will be placed in the EPIC electronic medical record. This will read “Patient XX has been randomized and placed in the Rescue Transesophageal Echocardiography for in-Hospital Cardiac Arrest (ReTEECA) trial and placed into one of two arms: Conventional CPR or Echo CPR. Randomization disclosure is possible if clinically necessary. Please contact study PI Asad Usman for this information. Any complications will be recorded and disclosed to the care team immediately.”

10.1.9.2 Study Records Retention

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an International Conference on Harmonization (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

Screening records for all IHCA subjects will be maintained. Patient information will be de-identified by software-based imaging techniques when imaging is analyzed. This encryption tool is available in all imaging-based storage systems. Imaging will be erased 5 years after the end of the study period.

10.1.10 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonization Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 7 working days of identification of the protocol deviation, or within 7 working days of the scheduled protocol-required activity. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

10.1.11 Publication and Data Sharing Policy

This study will be conducted in accordance with the following publication and data sharing policies and regulations: National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of the ReTEECA trial research. It requires scientists to submit final peer-reviewed journal manuscripts to the

digital archive PubMed central upon acceptance for publication. At the time of submission for this protocol there currently no NIH funding for this project. However, in the event of NIH funding, compliance with NIH funding publication policy will be followed.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial has been registered at ClinicalTrials.gov as trial NCT04220619 and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals.

This study will be used for several journal article publication and also help drive departmental policy in the Department of Anesthesiology and Critical Care – Cardiovascular Anesthesiology and cardiothoracic ICU section for POC TEE. We intend to submit separate work on the EFIC results including de-identified results from the clinician interviews and surveys, de-identified results from the patient and family interviews and surveys, and also bioethics works on EFIC and consent related topics in cardiac arrest. We intend to also submit for several research grants both through the NIH and also through the AHA.

After the conclusion of the ReTEECA trial period of 3 years the data is expected to be analyzed and published in various medical journals. We also intended to distribute the results of our study on the Penn Anesthesiology webpage. We will revisit community consultation both in the healthcare worker and non-medical layperson cohort with disclosure of the results of the ReTEECA trial. Public dissemination will occur through local and national broadcast (e.g., presentations, press releases). In particular we will post our results online including the Anesthesiology website and will follow up with our audio blog interviews and the Resuscitative TEE working group. Individuals who participated and have contact information will be informed of the results by a study coordinator.

10.1.12 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial.

10.2 Abbreviations

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities

MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

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Appendix

The Appendix is not available with this version.

Figures

Figure 1

Schema

Rescue Echo Protocol

Indications:

Refractory Hypotension
Hypoxia
EKG changes
Arrhythmias
Cardiac Arrest

Contraindications:

Esophageal stricture
Esophageal trauma
Esophagectomy

Events to Exclude

Shock state
Hypovolemic
Distributive
Cardiogenic

Tamponade

Tension Pneumothorax

Pulmonary Embolism

Myocardial Infarction

SAM/HOCM

Aortic Dissection

PFO (Hypoxia)

Exam Sequence

ME 4 Chamber

ME AV LAX

ME Bicaval

TG SAX

Aorta

Developed by Genevieve Staudt, MD and
Ken Shelton, MD.

Figure. Rescue Echo Protocol. TEE diagrams adapted from Reeves et al.¹ AV indicates aortic valve; EKG, electrocardiogram; HOCM, hypertrophic obstructive cardiomyopathy; LAX, long axis; ME, midesophageal; PFO, patent foramen ovale; SAM, systolic anterior motion of the mitral valve; SAX, short axis; TEE, transesophageal echocardiography; TG, transgastric.

Figure 2

See image above for figure legend.

Table. Continued		
Variable	Count (n = 48)	Percentage
Intervention ^a		
Cardiac catheterization	2	4.2
Cardiology consult	7	14.6
Case cancellation	6	12.5
ECMO	1	2.1
Fluid resuscitation	5	10.4
Imaging study	2	4.2
Inotropic support	2	4.2
Surgical intervention	4	8.3
Upgraded level of care	9	18.7
Vasopressor support	4	8.3
Other ^c	3	6.3
No change	13	27.1
Survival to discharge		
Yes	36	75.0
No	12	25.0
Complication related to TEE		
Yes	0	0
No	48	100

Abbreviations: ASA, American Society of Anesthesiologists; ECMO, extracorporeal membrane oxygenation; PE, pulmonary embolism; PFO, patent foramen ovale; SAM, systolic anterior motion of the mitral valve; TEE, transesophageal echocardiography.

^aAdditive percentage >100% as some patients had multiple indications for examination, findings, and interventions.

^bIncludes massive hemorrhage and suspected aortic dissection.

^cIncludes cardioversion, systemic anticoagulation, and allergy/immunology consult.

Figure 3

Legend not included with this version

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