**TITLE: Carolinas Cardiogenic Shock Initiative**

**Protocol #:** *Carolinas CS Initiative*

**LAY TITLE:** *Carolinas Cardiogenic Shock Initiative*

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The study will be conducted in compliance with the protocol, ICH-GCP and any applicable regulatory requirements.

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| **PROTOCOL SUMMARY** | |
|---|---|
| **Study Title** | Carolinas Cardiogenic Shock Initiative |
| **Study Design** | This is a case series and prospective patient registry |
| **Study Objectives** | To determine if deferred or delayed implantation of Impella device based on shock severity index is non-inferior with respect to 1 month and 1 year mortality compared to standard clinical protocols that do not differentiate based on shock severity in adult patients following an initial diagnosis of acute myocardial infarction complicated by cardiogenic shock (AMICS). |
| **Study Population** | The registry will include all eligible subjects from approximately 5/1/2019 until 4/30/2024, at participating sites. |
| **Study Procedures** | Adult patients with a diagnosis of AMICS will have their clinically available data contribute to the project registry. Patients who meet criteria for inclusion into the registry will have their chart reviewed periodically for the purposes of the registry, for proof of survival at one month and one year post-admission. Social Security Death Index (SSDI) data will be used to determine mortality at one month and one year if unable to confirm using the electronic health record. Patient clinical data will be pulled from the medical record and entered or migrated into a database for comparison and analysis. All data collected for the study will originate in the medical record from clinically available information, from a national death database, or from other publically available data sources. |

# LIST OF ABBREVIATIONS

| ABBREVIATION | DEFINITION |
|---|---|
| AMICS | Acute Myocardial Infarction complicated by Cardiogenic Shock |
| ANT | Anterior |
| CathPCI Registry | Catheterization and/or percutaneous coronary intervention registry |
| CS | Cardiogenic Shock |
| DUA | Data Use Agreement |
| DMP | Data Management Plan |
| eCRF | Electronic Case Report Form |
| ECMO | Extracorporeal Membrane Oxygenation |
| HFrEF | Heart Failure with reduced ejection fraction |
| HFpEF | Heart Failure with preserved ejection fraction |
| IABP | Intra-aortic balloon pump |
| ICU | Intensive Care Unit |
| INF | Inferior |
| LAT | Lateral |
| LBBB | Left bundle branch block |
| MCS | Mechanical Circulatory Support |
| MOP | Manual of Procedures |
| NCDR | National Cardiovascular Data Registry |
| PAPI | Pulmonary Artery Pulsatility Index |
| PCI | Percutaneous Coronary Intervention |
| PI | Principal Investigator |
| RHC | Right Heart Catheterization |
| STEMI | S-T elevation myocardial infarction |
| TIA | Transient Ischemic Attack |
| TTM | Therapeutic Temperature Management |

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# 1. OBJECTIVES

## 1.1. Hypotheses

A standardized clinical protocol that selects patients for MCS based on shock severity, will be non-inferior with respect to 1 month and 1 year mortality, compared to standard clinical protocols that do not differentiate based on shock severity in adult patients following an initial diagnosis of acute myocardial infarction complicated by cardiogenic shock (AMICS).

Those patients with shock that is not severe and do not have MCS, have a mortality rate that is similar or better than patients who have severe shock and receive MCS.

## 1.2. Primary Objective

The primary objective of this study is to contribute to the evidence base defining which types of patient with AMICS are likely to receive the most benefit from MCS.

## 1.3. Secondary Objectives

Secondary objectives include:

a. Develop and maintain a patient registry that includes electronic health record, administrative and patient reported outcomes data.
b. Classify patients based on shock severity.

## 1.4. Exploratory Objective

Further questions within the scope of the project may be examined using data within the registry, as a part of the exploratory analyses.

# 2. BACKGROUND

Cardiogenic Shock complicating acute myocardial infarction (AMICS) is associated with significant mortality, with rates ranging from 40-60% (Kolte et al.; Wayangankar et al., 2016). To date, only early mechanical reperfusion has been shown to have a significant impact on mortality (Hochman et al., 2001). Hemodynamic support is commonly employed in patients with more severe forms of shock, but there remains considerable debate regarding the need, type of device, and timing of deployment. Moreover, approaches in the United States and Europe differ widely (Thiele et al., 2015; O'Neill et al., 2017), and randomized trials have yielded results that have failed to clarify the optimal strategies, resulting in broad clinical variation in treatment with both cost and outcome implications.

In addition to prompt mechanical reperfusion, the most commonly utilized adjunctive hemodynamic support include intra-aortic balloon counterpulsation (IABP), the micro-axial Impella 2.5, CP, and 5.0 systems, and extracorporeal membrane oxygenation (ECMO). Intra-aortic balloon counter-pulsation remains the most widely used device, although the hemodynamic effects are quite modest, with limited improvement in cardiac output despite diastolic augmentation and afterload reduction (Kern & Sato, 2016). In the IABP Shock II trial, 600 patients were randomized in open label fashion to IABP vs. no IABP in addition to mechanical reperfusion. A majority of patients received IABP after reperfusion, and there was no impact on mortality at 30 days or one year (Thiele et al., 2012). Based on the results of this trial, the European guidelines have been updated with a Class III recommendation for IABP in cardiogenic shock with the US with a Class IIb recommendation (ESC/EACTS, 2014; Levine et al., 2016).

Impella is a trans-catheter axial flow pump that can be delivered percutaneously and can provide 2.5-5.0 L/min of forward flow depending upon the device used. While the use of Impella improves the degree of hemodynamic support compared to IABP (Seyfarth et al., 2008), in the open label randomized IMPRESS trial in 48 patients, short term mechanical circulatory support with Impella did not improve mortality compared to IABP, and was associated with multiple complications (Ouweneel et al., 2017). However, 92% percent of the patients presented with cardiac arrest and all required mechanical ventilation. In contrast, the USpella registry suggested that early initiation of hemodynamic support prior to PCI with Impella is associated with more complete revascularization and improved survival in the setting of refractory cardiogenic shock complicating acute myocardial infarction (O'Neill et al., 2014). Moreover, five Detroit area centers performed a pilot feasibility analysis to determine whether early routine use of mechanical circulatory support with Impella utilized before PCI is possible, and whether impact on outcomes could be tracked. Based on the early encouraging results, an algorithm with early MCS with Impella prior to PCI utilizing a structured de-escalation protocol has been launched as a national initiative (National Cardiogenic Shock Initiative).

Current clinical standards do allow for the delay of Impella implantation or based on the device materials or FDA approval or IDE marketing application/approval Impella is specifically for those with severe shock which outweighs the procedural risks and financial burden.

## 3. RATIONALE

Existing protocols in Europe and the United States vary widely based upon device selection and timing of support, a finding that is complicated by the limited data in a condition that is difficult to evaluate (Thiele et al., 2015; O'Neill et al., 2014; Diepen et al., 2017). Protocols in Europe suggest the deployment of MCS following revascularization, an approach which may underutilize a key pathway to better outcomes (O'Neill et al., 2014; Zeymar & Thiele, 2017; Brodie et al., 1999). In contrast, a significant concern for the National Cardiogenic Shock Protocol is that the existing

protocol may lead to Impella utilization in milder forms of shock when it may not be needed, resulting in potentially high artificial survival rates, unnecessarily expensive resource utilization, and life-threatening complications. Moreover, alternative devices, such as IABP or ECMO, may be more appropriate in specific clinical situations (small femoral anatomy, mitral regurgitation, RV failure, hypoxemia).

A recent American Heart Association Scientific Statement on the contemporary management of Cardiogenic Shock advocates for the development of regionalized systems of care and outlines future research priorities (Diepen et al., 2017). The statement notes that when, how, and which MCS device should be used remains unclear. Thus, outcomes of treatment in specialized cardiogenic shock centers which offer all treatment options, should be evaluated further.

The objective of the Carolinas Cardiogenic Shock Initiative will be to evaluate outcomes associated with utilization of MCS prior to PCI or delayed implementation in patients after reperfusion, based upon shock severity. An algorithm will be utilized which allows device variation based upon patient specific factors, employing a protocol driven approach to de-escalation in specialized shock centers with access to a variety of treatment options. Whether this can improve upon the protocol adopted by the National Cardiogenic Shock Initiative is unknown. However, the initiative addresses specific concerns that have arisen, leading to broad variation in the international approach to cardiogenic shock. A likely secondary benefit, is that a regionalized protocol should reduce center specific provider variation, allowing better outcome analysis and ability to execute specific protocol adjustments as a quality improvement initiative.

Previous research suggests that one of the only interventions to show a benefit to patient outcomes in adults who present with AMICS, is early mechanical reperfusion, with Impella being one of the more commonly used devices for treatment. However, variation exists across sites and facilities in patient survival rates and other clinical outcomes. Mechanical intervention also comes with its own risk. Implantation of Impella is an invasive and possibly risky procedure, with several possible side effects. There is also the possibility of the patient's financial burden from the admission and procedure.

Previous work has been done to identify key treatment elements which could be built into a widely accepted and utilized treatment algorithm for individuals who present with AMICS. However, further evaluation of comparing patient outcomes and treatment plans based on multiple aspects of the diagnosis, is needed to provide informed advice and guidance to patients. This project seeks to examine further diagnosis detail to determine if timed or delayed mechanical intervention is appropriate for patients with AMICS, based on shock severity.

# 4. INVESTIGATIONAL PLAN

## 4.1 Overall Study Design

The Carolinas Cardiogenic Shock Initiative is a clinical pathway and process improvement protocol already agreed upon by participating sites, to improve care by using a standardized algorithm to treat patients with AMI and CS. This prospective registry will capture data from this protocol as a multi-site research project in parallel with this standardized non-research clinic workflow protocol. Participating providers will follow the clinical protocol as standard of care for AMICS patients, as clinically appropriate. Patients who have been admitted and diagnosed with AMICS and meet all eligibility criteria will have their data entered in this registry.

All eligible patients will be entered into the registry and follow-up via the EMR and/or SSDI will occur at 30 days and one year to assess mortality. No additional provider appointments or further testing will be required as a part of this Registry, other than what each provider feels is medically necessary and indicated as a part of the patients' care plan.

Treatment decisions and timing will follow an approved clinical protocol and algorithm (see Appendix A) based on shock severity classification. The research team at each site will capture data generated during standard of care lab tests and clinical procedures, as well as data collected during clinical visits from eligible patients. Our target accrual is approximately 672 patients, cumulative across all participating sites.

Many of the patient specific outcomes and variables of interest for this study, are already submitted to the National Cardiovascular Data Registry (NCDR). Some additional data elements, as described in Apendix C, will also be captured. There are no benefits in participation other than the scientific knowledge gained, and the only alternative to participation is not participating.

### 4.1.1 Primary Outcome Variable

The primary outcome variable will be 30-day all cause mortality.

### 4.1.2 Secondary Outcome Variable(s)

Key secondary outcome variables for analysis may include but are not limited to:

- One year mortality
- length of ICU care
- requirement for renal replacement therapy
- dose and duration of catecholamine therapy

- requirement for implantation of an active LVAD or referral for cardiac transplantation
- time to support (arrival to tertiary facility to implantation)
- use of right heart catheterization
- Attainment of TIMI III flow post reperfusion
- Attainment of Cardiac power > 0.6 watts after completion of therapy
- Reduction or elimination of vasopressors and inotropic agents.
- blood products during admission
- hemolysis requiring device discontinuation
- vascular complication requiring surgery

## 4.2 Subject Selection

We have no reason to assume the patients who present with AMICS, will not be representative of the demographics of the region in which the participating site(s) are located. For this reason, we will not prioritize enrollment or recruitment based on demographics. Patients who present to the cardiac catheterization lab with AMICS at participating sites, and who meet inclusion criteria, will be included in the registry upon discharge. Data will be gathered in the usual manner for clinical purposes, for patients who die during their admission. The duration of the patient's enrollment in the registry is anticipated to last 1 year from AMICS. Recording of data in the registry is anticipated to last approximately five years.

### 4.2.1 Inclusion Criteria

**Subjects must meet all the following criteria:**

- Symptoms of acute myocardial infarction (AMI) with ECG and/or biomarker evidence of S-T elevation myocardial infarction (STEMI) or non-S-T elevation myocardial infarction (NSTEMI)
- Systolic blood pressure < 90mm at baseline or use of inotropes or vasopressors to maintain SBP > 90
- Evidence of end organ hypoperfusion
- Patient undergoes PCI

### 4.2.2 Exclusion Criteria

**Subjects must not meet any of the following criteria:**

- Evidence of Anoxic Brain Injury

- Unwitnessed out of hospital cardiac arrest or any cardiac arrest in which return of spontaneous circulation (ROSC) is not achieved in 30 minutes
- IABP placed prior to Impella
- Patient is already supported with an Impella
- Septic, anaphylactic, hemorrhagic, and neurologic causes of shock
- Non-ischemic causes of shock/hypotension (pulmonary embolism, pneumothorax, myocarditis, tamponade, etc.)
- Active bleeding for which mechanical circulatory support is contraindicated
- Recent major surgery for which mechanical circulatory support is contraindicated
- Mechanical complications of AMI (acute ventricular septal defect (VSD) or acute papillary muscle rupture)
- Known left ventricular thrombus for which mechanical circulatory support is contraindicated
- Mechanical aortic prosthetic valve
- Contraindication to intravenous systemic anticoagulation
- Receipt of thrombolytics with this event

### 4.3 Study Procedures

All inpatient data on eligible patients will come from the hospital inpatient records. Once the patient is deemed eligible, their clinical data will be entered or migrated into the research registry. Additional data will be collected at approximately one month and one year following AMICS, using the EMR and the SSDI.

The following are some of the variables which will be collected and recorded within the registry:

- Demographics
- Medical history
- Admission characteristics
- Diagnostic values
- Procedure dates and times
- Procedure characteristics
- Post-procedure information
- Discharge survival
- Survival at 1 month from AMICS
- Survival at 12 months from AMICS
- Additional Quality Metrics

### 4.4 Statistical Analysis

**4.4.1. Exploratory analysis.** Variable distributions will be examined using summary measures, tables, and graphics, such as histograms and scatter plots, where appropriate. Variables will initially be used as they were obtained; however, transformation may be

necessary or prove more informative. For example, continuous variables may be categorized, using common category boundaries found in the literature or based on percentiles of the variable distribution, in order to stratify the data. Student's t-test or the Wilcoxon rank-sum and chi-square statistics will be used to examine simple associations. For event history outcomes, we will primarily rely on survival analysis (i.e., event history modeling) to investigate if and when the event has occured (Singer & Willett, 1993). For this study, the time scale for mortality will be recorded in discrete time intervals (i.e., baseline, one month, one year); therefore, the underlying continuous time-to-event process will be modeled using discrete time.

A major consideration will be the nested organization of the data. Patients (level-1) are nested within sites (level-2). When hierarchical data are analyzed without regard to the interdependence of the data type-I error rates are inflated (aggregation) or deflated (disaggregation) resulting in incorrect significance tests and invalid conclusions (Hox, 2002). While multilevel modeling methods explicitly account for the nested structure of data, this approach is not feasible because we do not have sufficient number of sites to treat these effects as random (Hox & Roberts, 2010; Roberts, Monaco, Stovall, & Foster, 2011). Therefore, each site will be evaluated for differences in multiple group analyses. If the site differences are trivial, we will collapse the data across sites (Little, 2013). Non-trivial differences will require a grouping variable for site in subsequent analyses.

**4.4.2. Analytic strategy.** Insights gained from the exploratory data analysis will then be used to fit appropriate statistical models to the data. Within the context of survival analyses, we will begin by modeling the unconditional model (no covariates) in order to establish a baseline model. Next, we will add covariates with time-varying (nonproportional hazard odds) effects. Using model constraints, we will then fit a proportional hazard odds model and compare. Finally, we will probe for hypothesized effects.

Specifically, our goal is, first, to examine the degree to which a standardized clinical protocol that selects patients for MCS based on shock severity will be non-inferior with respect to mortality when compared with a standard clinical protocol that does not differentiate based on shock severity among adult patients following an initial diagnosis of AMICS. Second, our goal is to determine the degree to which mortality rates of patients with AMICS differ on MCS exposure.

*Missing Data*

Censoring will be assumed to be noninformative (i.e., the distribution of censoring times is independent of event times, conditional on the set of observed covariates). Missing data will be described in detail, including comparisons among participants that remained in the study to those that dropped out across demographic and outcome variables using t-tests, Little's MCAR test, or logistic regression (Nicholson, Deboeck, & Howard, 2015). Sensitivity analyses will be used to gauge the stability of inferences (Enders, 2010). When possible, we will use full-information maximum likelihood (FIML) estimation under the MAR missing data assumption (corresponding to the assumption of noninformative right

censoring) estimation option in the Mplus 7.3 software program to deal with missing data related to censoring and time-varying covariates with measurement intervals that do not correspond to the precision with which event times are measured. When appropriate, the robust standard error option, and the corresponding Satorra-Bentler correction for chi-square difference tests to evaluate site-level difference, will be used to correct for non-normality (Muthén & Masyn, 2005; Singer & Willett, 2003; Wang & Wang, 2012).

**4.4.2.1. Hypothesis 1.**

*Approach*

To evalaute this hypothesis, we will use a discrete time survival analysis (DTSA) within the structural equation modeling (SEM) framework (Muthén & Masyn, 2005; Raykov, Gorelick, Zajacova, & Marcoulides, 2017). This approach offers substantively important extensions to conventional DTSA models (e.g., logistic regression) that more accurately reflects the complexity and interconnectedness of survival (i.e., event history modeling) processes (Masyn, 2014). This more general approach includes the ability to model unobserved population heterogeneity (frailty) in the event history process, latent variable predictors of event history (e.g., health-related quality of life) including possible mediators and moderators, recurring events, competing risks, parallel and sequential growth processes (i.e., between-person variability in within-person change over time), onset-to-growth models, parallel event history processes, measurement error on event occurrence, hazard risk set matching, handling multilevel data structures, and time-varying covariate effects (non-proportional hazard) among other advantages (Masyn, 2013, 2014). Figure 1 presents an exemplary DTSA within the context of SEM (simplified for ease of presentation). In this example, three binary indicators (1, event occured; 0, event not occured) corresponding to the $j = 3$ proposed measurement occasions ($e_j$). In this analysis the hazard probability for a given measurement occasion will be defined as the probability of mortality in that occasion, provided that patient is alive. The hazard probability will then be related to time-varying ($w_j$) and time-invariant ($x$) covariates through a logit link function to parameterize the effect of a particular covariate on the log hazard odds of mortality during a given time interval. We will then describe covariate effects in terms of a hazard odds ratio (hOR). For example, if clinical protocol is coded 1 for typical and 0 for being based on a shock serverity score, were estimated to have a hOR of 2.0 at 30 days, we would note that the odds of mortality at 30 days for those without a shock severity protocol was twice the odds of mortality at 30 days for those with a shock severity protocol. This model can be written as: $logit\left(Pr\left(e_j = 1\right)\right) = \alpha_j + \beta_j x + \gamma_j w_j$, where $\alpha_j$ is the log hazard odds (with all covariates set to 0), $\beta_j$ is the difference in the log hazard odds and $exp\left(\beta_j\right)$ is the hazard odds ratio (hOR) for a positive one unit differece in $x$ (controlling for covariates $w_j$), and $\gamma_j$ represents a time-varying covariate effect for the difference in log hazard odds. The assessment of non-inferiority will be performed by comparing hazard odds ratio confidence intervals to the non-inferiority margin (Althunian, Boer, Groenwold, & Klungel, 2017). Specifically, since lower is better, non-inferiority will be concluded when the actual hazard ratio is less than the clinically acceptable ratio of 1.2.

*Power*
With respect to the 30-day primary end point of death, we estimated that an overall sample size of 672 patients would provide 80% power (at a one-sided alpha level of 0.025) to show the noninferiority of a standardized clinical protocol that selects patients for MCS based on shock severity to a standard clinical protocol that does not differentiate based on shock severity assuming the proportion of subjects observed with the event (death) during the study is 39.7% for the control group and 41.3% for the treatment group (Thiele et al., 2005; Thiele et al., 2013). The power was computed for the case when the actual treatment group proportion is 31%. The test statistic used is the one-sided Z test (unpooled).

*Expected results*
We expect a standardized clinical protocol that selects patients for MCS based on shock severity, will be non-inferior with respect to 1 month and 1 year mortality compared to standard clinical protocols that do not differentiate based on shock severity in adult patients following an initial diagnosis of acute myocardial infarction complicated by cardiogenic shock (AMICS).

*Potential problems and alternatives*
The issue of multiple testing that is involved in evaluating the p-values associated with a large set of covariates, is not addressed through the use of SEM. To address this concern, we will use the Benjamini–Hochberg (BH) procedure that is based on the false discovery rate concept, and has been shown to be more powerful than conventional multiple testing procedures (Benjamini & Hochberg, 1995; Benjamini & Yekutieli, 2001; Raykov, Lichtenberg, & Paulson, 2012). The inclusion of time-dependent covariates introduces reciprocal causation (Singer & Willett, 2003). We will address this issue by modeling covariate effects with a time-lag (Brown, 2012; Little, 2013). Model comparisons based on the Wald statistic test (dividing a parameter estimate by its standard error), may be influenced by non-normal concentration distributions (Little, 2013). To address this, we will use the adjusted likelihood ratio test statistic (i.e., Chi-Square Difference Test) using the log likelihood values and scaling correction factors obtained with the "MLR" estimator in Mplus, the default maximum likelihood estimator for binary and ordinal outcomes (Wang & Wang, 2012). In the event of unforeseen problems related to the proposed models, we will simplify our approach by modeling single-occurrence events in discrete-time with observed predictors using a multivariate logistic regression to model conditional model-estimated hazard probabilities and corresponding survival probabilities (Masyn, 2014; Muthén & Masyn, 2005). In this case, noninferiority will be calculated with the use of the Com–Nougue approach to estimating the z statistic for the Kaplan–Meier failure rates, with standard errors estimated by means of Greenwood's formula (Com-Nougue, Rodary, & Patte, 1993).

**4.4.2.2. Hypothesis 2.**

*Approach*
To evaluate this hypothesis, we will conduct a prevalence analysis using a multilevel regression model to obtain site-level prevalence estimates of participant mortality using the

general equation: $logit(p_{ij}) = X'\beta + \alpha_i$ , where $x_{ij} = (x_{ij1} \ldots x_{ijq})'$ is a vector of $q$ covariates, $\beta = (\beta_1 \ldots \beta_q)'$ is a vector of fixed effects and $\alpha_i$ is the random effect for site (Raudenbush & Bryk, 2002). The model will include demographic variables (e.g., race, gender, age, etc.), as well as site-level data and cross-level interactions. The prevalence estimates will be calculated from the predictors in the multilevel regression where: $\hat{p}_{ijk} = e^{predictor}/1 + e^{predictor}$. A follow-up evaluation will determine site-level prevalence rates by factors such as MCS and risk status categories, with the formula: $\hat{p}_{ijk} = \sum_j \frac{n_{ijkl}}{n_{ijk}} \hat{p}_{ijkl}$ , where $\hat{p}_{ijk}$ is the estimated prevalence of mortality in site *i* of risk status *j* at time *k*, $n_{ijkl}$ is the number of participants in site *i* that are of MCS (or risk status type) *j*, at time *k* and belong to demographic group *l* (i.e., a particular age, gender, race group), $n_{ijk}$ is the total population in site *i* of risk status type *j*, at time *k* and $\hat{p}_{ijkl}$ is the estimated prevalence of patient mortality in site *i* that are of risk status type *j* at time *k* and belong to demographic group *l*. We will compare these rates using risk difference and rate ratios (Agresti, 2013).

*Expected results*
We expect patients with shock that is not severe and do not receive MCS, have a mortality rate that is similar or better than patients who have severe shock and receive MCS.

*Potential problems and alternatives*
In the event of unforeseen problems related to the proposed models, we will simplify our approach by comparing the odds of mortality between groups using a multivariate logistic regression to model conditional model-estimated hazard probabilities and corresponding survival probabilities
(Masyn, 2014; Muthén & Masyn, 2005).

## 5. DATA AND SAFETY MONITORING PLAN

Data collected by the participating sites will be entered into case report forms, then stored and managed in a secure REDCap database hosted by Atrium Health. REDCap (Research Electronic Data Capture) is a secure, web-based application, designed to support data capture for research studies. The REDCap database which will be used for the registry, was built solely for the purposes of this project, and includes only those data elements deemed relevant for measuring and analyzing the objectives of interest.

The protocol and recorded data will be monitored in accordance with the Data Coordinating Center's monitoring plan, and will operate under standard operating procedures set forth by both the Office of Clinical and Translational Research and the Center for Outcomes Research and Evaluation at Atrium Health.

Due to the nature of this project, participation in the registry presents no more than minimal risk to subjects. According to the FDA Guidance for Clinical Sponsors: Establishment and

Operations of Clinical Trial Data Monitoring Committees, this study does not require oversight by a Data and Safety Monitoring Committee.

### 5.1. Data Quality Assurance

This study will be organized, performed, and reported in compliance with the study protocol, standard operating procedures (SOPs) set forth by the Office of Clinical and Translational Research and the Center for Outcomes Research and Evaluation at Atrium Health, the FDA, and other applicable regulations and guidelines (e.g. GCP).

Data will be collected on electronic Case Report Forms (eCRFs).

The protocol and recorded data will be monitored in accordance with the Data Coordinating Center's monitoring plan. This monitoring will be done by comparing source documentation to the eCRFs.

The study database will be reviewed and checked for omissions, apparent errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification will be generated and addressed by the appropriate research teammates, including the Project Coordinator and/or Principal Investigator. Only authorized personnel will make corrections to the project database, and all corrections will be documented in an electronic audit trail.

Any variation between the two data sets will be discussed with the site's Project Coordinator and Principal Investigator.

### 5.2. Communication Between Sites

The project steering committee and/or research team will meet on at least a monthly basis, or more frequently as needed. The meetings will take place to discuss any encountered issues, discuss project progress, and to address other project related topics, as appropriate.

Participating sites will be required to report any problem that could affect the validity/integrity of the study data to the Principal Investigator and the Data Coordinating Center. Any problem should be communicated to the Principal Investigator and the Data Coordinating Center as soon as possible.

## 6. STUDY COMPLETION

### 6.1 Completion

The study will be considered complete upon the determination of the Principal Investigator or the Institutional Review Board.

### 6.2 Termination

The study will be terminated upon completion of the enrollment period, or once the risk-benefit ratio becomes unacceptable owing to, for example, results of parallel studies or if the study conduct (e.g. data quality, protocol compliance) does not suggest a positive contribution toward the study objectives.

The Principal Investigator has the right to close the study at any time. Closures should only occur after consultation between involved parties and all affected institutions must be informed as applicable according to local law.

## 7. RETENTION OF RECORDS

Essential protocol documentation, including all IRB correspondence, will be retained for at least 2 years after the investigation is completed. Documentation will be readily available upon request.

## 8. ETHICAL AND LEGAL ISSUES

### 8.1 Ethical and Legal Conduct of the Study

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the Investigator abide by Good Clinical Practice (GCP) guidelines and under the guiding principles detailed in the Declaration of Helsinki. The study will also be carried out in keeping with the applicable local laws and regulation(s).

Documented approval from appropriate agencies (e.g. IRB) will be obtained before the start of the study, according to GCP, local laws, regulations, and organizations.

Strict adherence to all specifications laid down in this protocol is required for all aspects of study conduct; the Investigators may not modify or alter the procedures described in this protocol.

Modifications to the study protocol will not be implemented without consulting the Principal Investigator and the IRB, as applicable. The Principal Investigator must assure that all study personnel, including sub-investigators and other project staff members at external sites, adhere to the study protocol and all applicable regulations and guidelines regarding research both during and after study completion.

The Principal Investigator will be responsible for assuring that all the required data will be collected and properly documented.

## 8.2 Confidentiality

Subject confidentiality will be maintained by the Principal Investigator, the Investigator's associates and co-workers. Confidentiality will be maintained according to ICH E6; 4.8.10, part O: "Records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the study trial are published, the subject's identity will remain confidential."

Participation in the project registry presents no risk, other than breach of confidentiality. To mitigate this risk, only necessary patient identifiers will be captured, and all data used for the project will be stored in a secure REDCap database.

## 8.3 Disclosure of Data

The Principal Investigator, his or her associates and teammates, and the appropriate regulatory agencies may use the information and data included in this protocol as necessary for the conduct of the study. Information contained in this study, and data and results from the study are confidential and may not be disclosed without the written permission of the Principal Investigator.

Local Site Investigators and their research teams will only be able to access PHI from their own patients. However, Lead site teammates and other Project Team and Steering Committee Members may have access to the full registry data, inclusive of external site patient information, as appropriate for the purposes of data accuracy and project oversight. The following project team members will have access to patient medical information, and any necessary information for the completion of the project as outlined in the MOP and this protocol. Data Use Agreements will also be completed for participating sites external to the Coordinating Site's Healthcare System.

Atrium Health:

- PI
- Co-Investigator(s)
- Data Manager(s)
- Research Nurse(s)
- Data Coordinator(s)
- Statistician(s)
- Other Administrative Teammates such as Steering Committee or Project Team Members

External Sites:

- Local PI
- Sub-Investigator(s)

- Research Nurse(s)
- Data Coordinator(s)

## 9. PUBLICATION POLICY

There is no planned interim analysis of the data. A final analysis is planned, for the purpose of presentation and submission for publication of all data at the end of the study enrollment and follow-up periods.

Manuscript(s) and abstract(s) prepared from the data collected during this study will be prepared by the Principal Investigator and select members of the research team. Local Site Investigators will not publish or present results, for reasons beyond site care and quality improvement, without written consent of the Lead Principal Investigator, per the site DUA. Investigators will provide the Principal Investigator with publication or presentation materials (including slides, text of oral or written presentations, and electronic media), at least 30 days in advance of publication/presentation, to allow for review and comment as a means of ensuring confidentiality, accuracy, and objectivity.

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# APPENDICES

## *APPENDIX A: Cardiogenic Shock Algorithm*