HIGH-SENSITIVITY CARDIAC TROPONIN T TO OPTIMIZE CHEST PAIN RISK STRATIFICATION (STOP CP)

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Approvals:

This document outlines the clinical study high-Sensitivity cardiac Troponin t to Optimize Chest Pain risk stratification (STOP CP).

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1. STUDY SYNOPSIS

Task	Description
Title of Study	High-Sensitivity Cardiac Troponin T to OPtimize Chest Pain Risk Stratification (STOP CP)
Protocol Number	STOP CP001
Sponsor Product	Roche Diagnostic Generation 5 cTnT Assay
Study Team	**Co-Principal Investigator(s):** Allen, Brandon, MD, FACEP Mahler, Simon, MD, MS, FACEP **Co-Investigators:** Nowak, Richard, MD, FACEP McCord, James, MD, FACC Christenson, Robert, MD Wilkerson, Gentry R., MD Tyndall, Joseph Adrian MD, MPH, FACEP Payton, Thomas, MD, MBA, FACEP Elie, Marie-Carmelle, MD, RDMS, FACEP Winchester, David E, MD, MS, FACP, FACC (adjudicator) Riley, Robert, MD, FACC (adjudicator) Mumma, Brynn, MD, MAS Marchick, Michael, MD Shuster, Jonathan, PhD

Study Sites	**Study Coordinating Center** University of Florida (Gainesville, FL) **Participating Study Sites**: Wake Forest University (Winston-Salem, NC) Henry Ford Health System (Detroit, MI) University of Maryland (Baltimore, MD) UC Davis (Sacramento, CA)
Objectives	**Primary Aim:** Establish the performance (safety and efficacy) of Roche hs-cTnT in a cohort of US ED patients with acute chest pain. **Sub-aim 1:** Evaluate the sensitivity and specificity of established cut points including gender/age-specific cut points for the Roche hs-cTnT assay for MACE at 30 and 90 days. **Sub-aim 2:** Test whether a modified HEART Pathway (a HEART Score combined with single or serial Roche hs-cTnT) can safely identify >60% of patients for early discharge from the ED without stress testing or coronary CT angiography (CCTA). **Sub-aim 3:** Evaluate whether a new decision aid derived using logistic regression of clinical variables (such as patient demographics, chest pain features, cardiac risk factors, and ECG characteristics) plus the Roche hs-cTnT can achieve a higher early discharge rate than a modified HEART Pathway strategy while maintaining a ≥99% sensitivity for MACE at 30 and 90 days.
Study Design	This trial is designed as a multi-center prospective observational study enrolling subjects with acute chest pain. Clinical data and serial blood samples at 0, 1, 2, and 3 hours will be collected from each participant. Subjects will be contacted 30 days and 90 days after discharge.
Number of Subjects	Estimated 1,500 adult ED patients from 6 sites over an 18-month enrollment period.
Criteria for Inclusion	**Inclusion Criteria** 1. Age greater than or equal to 21 years of age at the time of enrollment in the ED. 2. Chest discomfort or other symptoms consistent with possible ACS in which the treating physician plans to obtain an ECG and cTn for the patient's evaluation in the ED. **Exclusion Criteria**

	1. New ST-segment elevation consistent with myocardial infarction. 2. Evidence of shock identified by the provider at the bedside and/or the PI. 3. Terminal diagnosis with life expectancy less than 90 days. 4. A non-cardiac medical, surgical, or psychiatric illness determined by the provider to require admission. 5. Prior enrollment in the STOP CP study. 6. Lack of capacity to provide consent and comply with study procedures. 7. Inability to be reliably reached after the index visit for follow-up. 8. Non-English speaking. 9. Pregnant patients. 10. Provider does not intend on obtaining serial cTn assays for evaluation of ACS. 11. The first study draw (T0) will exceed 1 hour after the site-specific standard of care troponin draw. 12. Unable or unwilling to authorize medical records release.
Subject's participation duration	90 + 30 days for follow-up

2. GLOSSARY

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS	
ACS	Acute Coronary Syndrome
ADP	Accelerated Diagnostic Protocol
AE	Adverse Event
AMA	Against Medical Advice
AMI	Acute Myocardial Infarction
ASA	Aspirin
CABG	Coronary Artery Bypass Graft
CAD	Coronary Artery Disease
Cath	Catheterization
CCC	Clinical Coordinating Center
CDU	Clinical Decision Unit
CHF	Congestive Heart Failure

CMR	Cardiac Magnetic Resonance
CMS	Center for Medicare/Medicaid Services
Co-I	Co-investigator
CP	Chest pain
CRF	Case Report Form
CT	Computed Tomography
cTn	Cardiac Troponin
CV	Curriculum vitae
CVA	Cerebral Vascular Accident
DM	Diabetes Mellitus
ECG	Electrocardiogram
Echo	Echocardiography
eCRF	Electronic Case Report Form
ED	Emergency Department
EDC	Electronic Data Capture
FDA	Food and Drug Administration
GERD	Gastroesophageal Reflux Disease
HIPAA	Health Insurance Portability and Accountability Act
HLD	Hyperlipidemia
hs-cTn	High sensitivity cardiac troponin
hs-cTnT	High sensitivity cardiac troponin T
HTN	Hypertension
IC	Informed Consent
ICU	Intensive Care Unit

I-DSMB	Institutional Data Safety Monitoring Board
IRB	Institutional Review Board
IV	Intravenous
JVD	Jugular Venous Distention
LAD	Left Anterior Descending
LBBB	Left Bundle Branch Block
LMCA	Left Main Coronary Artery
MACE	Major Adverse Cardiac Event
MI	Myocardial Infarction
MOP	Manual of Procedure
MRI	Magnetic Resonance Imaging
NIH	National Institutes of Health
NP	Nurse Practitioner
NTG	Nitroglycerin
OHRP	Office for Human Research Protections
OTC	Over-the-Counter
OU	Observation Unit
PA	Physician Assistant
PCI	Percutaneous Coronary Intervention
PHI	Protected Health Information
PI	Principal Investigator
PVD	Peripheral Vascular Disease
RBBB	Right Bundle Branch Block
RCA	Right Coronary Artery

RVU	Relative Value Unit
SAE	Serious Adverse Event
SAE	Serious Adverse Event
SOP	Standard Operation Procedure
STEMI	ST Elevation Myocardial Infarction
T0	T0 will be defined by the sufficient amount of blood obtained from the study subject by either initial clinical blood draw or subsequent sample collection after informed consent
T1	One hour after T0 +/- 30 minutes
T2	One hour after T1 +/- 30 minutes
T3	One hour after T2 +/- 30 minutes
TIMI	Thrombolysis in Myocardial Infarction
TnI	Troponin I
ULN	Upper Limit of Normal

3. BACKGROUND AND RATIONALE

Approximately 8 million – 10 million patients complaining of chest pain present to an Emergency Department (ED) annually in the United States. [1–3] To avoid missing the diagnosis of acute coronary syndrome (ACS), physicians use a liberal testing strategy. Thus, >50% of ED patients with acute chest pain are hospitalized for a comprehensive cardiac evaluation (serial cardiac biomarkers and stress testing or angiography). However, <10% of these patients are ultimately diagnosed with ACS, and this pervasive over-triage costs an estimated $10 billion – $13 billion annually.[1,2,4] Current care patterns for acute chest pain fail to focus health system resources, such as hospitalization and stress testing, on patients most likely to benefit.

Our study team has demonstrated that an accelerated diagnostic protocol (ADP), called the HEART Pathway, which utilizes a clinical decision aid (the HEART score in Table 1) and serial cTn measures are sensitive for ACS (>99%) and can substantially reduce hospitalizations, stress testing, and cost compared to usual care.[1-5] The HEART Pathway uses contemporary serial cTn measurements at 0 and 3 hours to exclude index MI and relies on clinical features (history, ECG, age, and risk factors) to identify patients likely to have downstream events. However, the HEART Pathway has limitations: a) It identifies only 20 – 40% of patients for early discharge and b) it was developed before high-sensitivity cTn assays became available. Able to detect MI earlier and with greater accuracy than contemporary assays, hs-cTn assays have the potential to be integrated into decision aids to improve chest

pain risk stratification. In the near future, hs-cTn assays will replace contemporary assays in the United States.

Table 1. The HEART score; Low-risk= 0-3, High-risk= 4 or greater.

		Points
History	Highly Suspicious	2
	Moderately Suspicious	1
	Slightly Suspicious	0
ECG	Significant ST-depression	2
	Non-specific repolarization abnormality	1
	Normal	0
Age	≥ 65	2
	45-65	1
	< 45	0
Risk factors	3 or more risk factors	2
	1-2 risk factors	1
	No risk factors	0
Troponin	≥ 3x normal limit	2
	1-3x normal limit	1
	≤ normal limit	0
Total		

To fully capitalize on the improved sensitivity of the hs-cTn assays, decision aids (like the HEART Pathway) must be reengineered or replaced to increase the proportion of patients identified for early discharge while maintaining high sensitivity for cardiac events. A recent study by Bandstein et al suggests that many patients can be identified as low-risk based on an initial undetectable Roche hs-cTnT (<5 ng/L).[6]

However, among patients with detectable biomarkers, hs-cTnT measures < 99th percentile upper reference limit (5-14 ng/L), only 3% suffered adverse cardiac events.[6] These data suggest that an opportunity exists to safely achieve higher (>80%) early discharge rates by combining Roche hs-cTnT values with clinical variables.

4. STUDY OBJECTIVES

Primary Aim:

Establish the performance (safety and efficacy) of Roche hs-cTnT in a cohort of US ED patients with acute chest pain.

Sub-aim 1:

Evaluate the sensitivity and specificity of established cut points including gender/age specific cut points for the Roche hs-cTnT assay for MACE at 30 and 90 days.

Sub-aim 2:

Test whether a modified HEART Pathway (a HEART Score combined with single or serial Roche hs-cTnT) can safely identify >60% of patients for early discharge from the ED without stress testing or coronary CT angiography (CCTA)**.**

Sub-aim 3:

Evaluate whether a new decision aid derived using logistic regression of clinical variables (such as patient demographics, chest pain features, cardiac risk factors, and ECG characteristics) plus the Roche hs-cTnT can achieve a higher early discharge rate than a modified HEART Pathway strategy while maintaining a ≥99% sensitivity for MACE at 30 and 90 days.

5. OVERVIEW OF STUDY DESIGN

This is a prospective observational cohort study of ED patients with acute chest pain or other symptoms suggestive of ACS. Blood samples will be collected from study participants for hs-cTnT analysis. Results from hs-cTnT will be used for research purposes only.

Providers will be blinded to results and participants will be treated by their healthcare providers per the standard of care. Participants will have 30 and 90-day phone follow-ups to ascertain study outcomes.

5.1 Rationale for Study Design

The performance of the Roche proposed hs-cTnT cut points derived in the recent submission to the FDA will be tested initially as well as gender and age-specific cut points and cut points established in prior studies. Measurements of hs-cTnT will then be integrated into the HEART Pathway to test, refine, and optimize the modified HEART Pathway's performance. Finally, the performance of a novel decision aid which incorporates hs-cTnT measures will be tested to see if it outperforms the modified HEART Pathway when used alone. This approach will determine an optimal decision aid integrating the Roche hs-cTnT assay.

5.2 Blinding

Blood samples will be collected from study participants for hs-cTnT analysis. Results of hs-cTnT will be used for research purposes only. Providers and participants will be blinded to results and participants will be treated by their healthcare providers per the standard of care. See section 8 for Blood Sample Procedures and Materials.

5.3 Duration

The duration of subject participation is expected to be approximately 90 but no more than 120 days following date of study enrollment and consent in order to facilitate follow-up visits.

5.4 Regulatory Compliance

The study will be conducted in compliance to this study protocol, the current version of the Declaration of Helsinki, ICH, GCP, and applicable local legal regulatory requirements.

5.5 Risks and Benefits

There is no direct health benefit in participating in this study. Study results will not be made available to the medical personnel and participant at the site. The only study-related procedures that could affect subject safety are the blood draws to obtain the blood samples required for testing. The risk of drawing blood via venipuncture may include dizziness/fainting, pain, bleeding and bruising at the site of the of the blood draw. Infection at the site of the blood draw is a rare complication. The amount of blood drawn specifically for this study is no more than what is expected during standard of care procedures and not expected to pose a significant risk to the participant.

No genetic testing will be performed on any sample. Left over blood samples may be used for future research.

6. STUDY SUBJECTS

6.1 Number of Subjects

The study is projected to include n=1,500 subjects.

Based on these data, we expect the biomarker in conjunction with the HEART pathway to have 60% of patients classified as “Good Prognosis” (MACE Rule out). We shall estimate the MI rate in this group by an exact one-sided 95% confidence interval for the probability of an MI in the rule-out group. With 1,500 subjects, we expect this to be based on n=1,200.

6.2 List of Study Sites

The list of the study sites participating in this study:

- **Study Coordinating Center**

  University of Florida (Gainesville, FL) — Allen, Brandon, MD (Principal Investigator)

- **Participating Study Sites**

  Wake Forest University (Winston-Salem, NC) — Mahler, Simon, MD, MS (Principal Investigator)

  Henry Ford Health System (Detroit, MI) — (Nowak, Richard, MD)

  University of Maryland (Baltimore, MD) — (Wilkerson, Gentry, MD)

  UC Davis (Sacramento, CA) — (Mumma, Brynn, MD)

- **Central Processing Site**

  University of Maryland (Baltimore, MD) — (Christenson, Robert, MD)

This list is subject to change and will be maintained by the project coordinator for the duration of the trial. Before commencing the study at each site, the name of the

investigator as well as the evidence of investigators' competence and skills (e.g., CV and medical license, if applicable), shall be collected and maintained in the study regulatory binder. Each Principal Investigator will be required to sign and date the "Statement of Investigator" included at the end of this protocol signifying agreement to the terms and condition set forth in this protocol.

6.3 Inclusion Criteria

1. Age greater than or equal to 21 years at the time of enrollment in the ED
2. Chest discomfort or other symptoms consistent with possible ACS in which the treating physician plans to obtain an ECG and cTn for the patient's evaluation in the ED

6.4 Exclusion Criteria

1. New ST-segment elevation consistent with myocardial infarction
2. Evidence of shock identified by the provider at the bedside and/or the PI
3. Terminal diagnosis with life expectancy less than 90 days
4. A non-cardiac medical, surgical, or psychiatric illness determined by the provider to require admission
5. Prior enrollment in the STOP CP study
6. Lack of capacity to provide consent and comply with study procedures
7. Inability to be reliably reached after the index visit for follow-up
8. Non-English speaking
9. Pregnant patients
10. Provider does not intend on obtaining serial cTn assays for evaluation of ACS
11. The first study draw (T0) will exceed 1 hour after the site-specific standard of care troponin draw
12. Unable or unwilling to authorize medical records release

6.5 Subject Enrollment

We anticipate 1,800 subjects will be approached in order to achieve the goal of 1,500 subjects.

6.6 Subject Exclusion from Primary Analysis and Replacement

Criteria for exclusion from the primary analysis include:

1. Inability to obtain a serial cTn measure 2-12 hours after the initial blood draw as part of routine clinical care, except in patients with an initial positive cTn measure
2. Failure to obtain at least two study-specific blood samples within the protocol timeframe detailed in section 7.4-7.8 and 8.1-8.4

We will replace any subjects meeting the exclusion from analysis criteria above until the goal enrollment of 1,500 subjects is reached across all sites.

7. STUDY PROCEDURES

7.1 Recruitment

- **Screening Procedures:** Patients who present to a study site with symptoms suggestive of acute coronary syndrome will be screened for inclusion and exclusion criteria as allowed by the Western Institutional Review Board (WIRB) or each site's IRB. Research team members will screen patients using partial waiver of HIPAA authorization, and patients who meet criteria for inclusion and who are willing and able to provide written informed consent will be enrolled into the study. The study will be approved by an IRB at each site prior to site enrollment.
- The release of medical records form should be collected at the time of subject consent.
- Contact information will be collected from the subject at the time of consent including their telephone number of the subject, the telephone number of a close relative or caregiver, mailing or physical address, electronic mail, and the preferred mode of contact.

7.2 Screening Procedures

- All female enrolled subjects of childbearing potential will have a documented pregnancy test. Those female subjects under the age of 55 years without childbearing potential will have documentation by the study staff of the reason including hysterectomy or postmenopausal status. Results from pregnancy tests performed within 7 days of the index visit may be used if available. Any tests not collected clinically must be obtained according to the protocol.
- Enrolled subjects that meet exclusion criteria or do not meet inclusion criteria and do not complete any study procedures (i.e., blood draws) will be considered screen failures and will discontinue all further participation.

7.3 Data Collection

- The study will utilize an electronic data capturing tool for all study subject data collection across all sites.
- Study personnel will collect data regarding presenting symptoms at the time of arrival to the ED from the care provider and additional data may be directly collected from the subject. Each historical element for the HEAR score will be documented by indicating the source of the data, i.e. provider, patient, medical record. ED providers of each subject will be asked to complete a HEAR score based on the HEART pathway.
- These values may be obtained from clinically collected information at the time of index visit.

7.4 Blood Draws

Study participants will have a blood draw on arrival as part of standard care. Since the first blood draws are often collected prior to the time of consent, following enrollment, the research team must obtain left over blood from previously collected samples for processing. As part of informed consent, participants will provide consent to obtain blood via separate venipuncture or draw from an existing intravenous line for the T0 hs-cTnT analysis if insufficient blood is able to be obtained from the initial blood draw as part of standard care. Additional blood draws will be collected via separate venipuncture or draw from an existing intravenous line on participants at T1, T2, and T3 time intervals as described below. Blood samples will be processed and shipped for testing and storage in Baltimore, Maryland at the University of Maryland; providers will be blinded to hs-cTnT results. The hs-cTnT results will be provided by the University of Maryland core site laboratory to be inputted into the electronic data capture system. The blood samples will be de-identified and have a specific study participant number to correspond to the patient.

7.5 Blood Draw at Baseline T0

Baseline blood samples are considered the first blood draw which corresponds most closely with the initial medical evaluation by a health care provider in the emergency department. Since the first clinical blood draws are often collected prior to the time of consent, following enrollment, the research team must obtain left over blood from previously collected samples for the T0 hs-cTnT analysis. Local research teams will be responsible for following local procedure for procuring left over blood specimen following standard of care sampling. If insufficient blood is available from the initial standard of care blood draw, a sample of blood via separate venipuncture or draw from an existing intravenous line will be performed for the T0 hs-cTnT analysis. A blood tube will be obtained for sampling and preparation for shipping to the core laboratory in Maryland for hs-cTnT processing. Baseline time T0 will be defined by the timing of the blood draw that is considered sufficient for sample analysis of hs-cTnT and cannot exceed 1 hour of the site-specific standard of care troponin draw.

7.6 Blood Draw at T1 (1 hour after T0 +/- 30 minutes)

Blood will be obtained one hour after T0 +/- 30 minutes. The research team will obtain one lithium heparin tubes and one EDTA tube for sampling and preparation for shipping to the core laboratory in Maryland for hs-cTnT processing.

7.7 Blood Draw at T2 (1 hour after T1 +/- 30 minutes)

Blood will be obtained at one hour after T1 +/- 30 minutes. The research team will obtain one lithium heparin tubes and one EDTA tube for sampling and preparation for shipping to the core laboratory in Maryland for hs-cTnT processing.

7.8 Blood Draw at T3 (1 hour after T2 +/- 30 minutes)

Blood will be obtained at one hour after T2 +/- 30 minutes. The research team will obtain one lithium heparin tubes and one EDTA tube for sampling and preparation for shipping to the core laboratory in Maryland for hs-cTnT processing.

7.9 Clinical Assessment

Each participant will receive standard medical care blinded to hs-cTnT results. Patients presenting with chest pain or other symptoms concerning for ACS are expected to undergo a clinical assessment that includes medical history, physical examination, 12-lead ECG, and diagnostic blood testing, including site-specific cTn as part of the standard of care. Levels of site-specific cTn are typically measured at presentation and serially thereafter for as long as clinically indicated. Further treatment, testing, and disposition decisions will be at the discretion of the provider in keeping with local protocols and practice patterns.

7.10 Post Discharge Data Collection

After discharge, data from the date of enrollment, including results of diagnostic testing, invasive procedures, and diagnoses, will be explicitly abstracted by the study team from the electronic data capture. ECG data will be classified by an investigator.

7.11 Follow-Up Visits

Study staff will review patient medical records at 30 and 90 days using a structured data abstraction template to detect events occurring at that facility since the last follow-up period. Study staff will then contact participants by telephone at 30 (+10 days) and 90 days (+30 days) using a modified version of a previously described scripted follow-up dialogue to further clarify events since discharge, identify events occurring at other care facilities, and determine health care utilization since discharge.[8] Participants reporting potential cardiac-related events at other facilities will have their records requested from that facility, and the data will be reviewed using the same structured data abstraction template.

- At 30 (+10) and 90 (+30) days after enrollment, participants will be contacted to determine clinical outcomes (death, acute myocardial infarction, or coronary revascularization), cardiac testing, recurrent ED visits, re-hospitalizations, and adverse events by study staff blinded to cTnT results and HEART scores. Adverse events reported by patients that occurred at outside facilities will be confirmed by medical record request.
- Participants unable to be contacted after three attempts will be contacted using alternative contact methods provided during enrollment (email, text, emergency contact number, etc.) and if still unsuccessful, will be sent a letter to their listed address. Unsuccessful follow-up attempts at 30 (+10 days) will be followed by repeating the follow-up procedure at 90 (+30) days unless the methods of contact have been determined to be invalid. Participants still unable to be contacted will be considered censored at their last known contact unless record review reveals an event occurred, in which case the patient will be considered to have experienced an event. Participants unable to be contacted will be searched for in the Social Security Death Master File. In the event of discrepancy between a participant's event reporting and the medical record, the medical record will be considered correct.

7.12 Adjudication process

A consensus of two reviewers will adjudicate elements required to measure the occurrence of MACE. To make these assessments, reviewers will be provided the participant's index and discharge records, follow-up call information, records obtained from follow-up, and study definitions. Records will have patient identifiers and randomization group identifiers removed. Reviewers will complete a reviewer outcome form recording the occurrence of these endpoints, which will be placed in the participant binder. Any disagreements will be settled by consensus between the two reviewers, or the involvement of a third reviewer.

Table 2. Schedule of Events

	Screen	T0	T1	T2	T3	30 day follow up (+ 10 days)	90 day follow up (+ 30 days)
Evaluation/Procedure							
Eligibility							
Informed Consent	x						
Pregnancy Test (for females of childbearing potential)	x						
Inclusion Criteria	x						
Exclusion Criteria	x						
Demographics and Medical History	x						
Study Procedures							
Clinical Data[1]		x	x	x	x	x	x
One blood tube for processing (heparin or EDTA)		x					
Site-specific cTn at T0		x					
Site-specific cTn at T3[2]					x		
One Lithium Heparin blood tubes for hsTnT		x	x	x	x		
One EDTA blood tube for hsTnT		x	x	x	x		
Adverse Events		x	x	x	x	x	x

1. Every patient must have an ECG, documented history and physical examination, HEAR score calculation, and site-specific cTn at T0 and T3.
2. Serial troponins required unless initial site-specific cTn positive.

8. SAFETY CONSIDERATIONS

The Investigator for each site will be responsible for monitoring the safety of subjects who enter this study and for documenting and reporting all Adverse Events to the sponsor. There will be an unbiased medical monitor assigned to the study to ensure the safety of subjects. As this is an observational study with minimal risk rather than interventional study a serious adverse event (SAE) related to study procedures is unlikely.

8.1 Blood Draws

Subjects participating in this study shall be under minimal risk. The only study-specific procedure that could impact subject safety is the blood draws to obtain study-specific blood samples. Blood sampling that involves simple venipuncture is considered non-invasive according to 21 CFR Par 81.3(k).

The risks of drawing blood via venipuncture may include pain, bleeding, bruising or swelling at the site of the blood draw or lightheadedness or syncope. Infection at the site of the blood draw is also a rare complication. Whenever possible, study-specific blood samples will be drawn at the same time as routine blood draws or will be obtained via existing intravascular access lines to minimize the need for additional study-related venipunctures. In addition, to decrease volume of blood drawn, the baseline blood draw may be obtained from leftover specimen used as standard of care, if an adequate sample is available.

Anemia and related complications (dyspnea, hypoxia, etc.) may be associated with withdrawal or loss of large amounts of blood. However, the amount of additional blood drawn specifically for the biomarker measurements (less than or equal to 20 mL) represents a small percentage of blood and is not expected to pose a significant risk to the subject. We will mitigate risk and recognition of patients with a previous history of anemia.

There is no direct benefit of this study to the enrolled subjects because the information obtained is for observational use only and the providers will remain blinded to the results.

8.2 Information Disclosure

There is a risk of personal health identifier disclosure as part of participation in this study. All samples and study records will be coded using study-specific IDs. No personal identifiers (name, address, SSN, MR#) will be shared. This study protocol, documentation data, and all other information will be held in strict confidence by the Investigator and his or her representatives. In addition, all PHI will be stored on secure servers at each of the respective investigational sites to minimize exposure. Site specific PHI will be only available to the site, so that while access to clinical data will be available, all other sites will be blinded to identifiers such as name, medical record identifiers, or contact information. All study and source documents will be maintained by the investigator for a period of at least 2 years after the investigation is terminated or

completed or for a period of 2 years after the records are no longer required or for a period greater than 2 years if required by the local institution's IRB.

8.3 Adverse Events

Safety Reporting

Timing of assessments

Evidence of adverse events will be assessed at each visit. SAE's are unlikely to be related to this study and the PI will review them on a case-by-case basis.

Timing of reporting

Please refer to flowchart.

Criteria and definitions

Our patient population may be clinically stable to critically ill. It is expected that critically ill subjects will have a number of unrelated adverse health events during the course of their hospital stay. Therefore, we will limit the scope of study AE monitoring and recording to the following:

Serious Adverse Events, defined as:

- Death, believed to be related to the study or procedures, or a death that is unexpected considering the acuity of a patient.
- A life-threatening experience believed to be related to the study or procedure.
- Persistent or significant disability or incapacity that is of greater frequency or severity than what would be normally expected in the course of critical illness.
- An event that jeopardizes the Human Subject and may require medical or surgical treatment to prevent one of the preceding outcomes and is not expected in the course of illness.

Adverse Events possibly related to blood draws

- Hematoma
- Excessive bleeding
- Infection at the venipuncture site
- Thrombophlebitis
- Lightheadedness or syncope

Unanticipated Problems

An unanticipated problem is not necessarily an adverse event if no patient is harmed. Examples include a breach of confidentiality (e.g. laptop gets lost) without direct harm to patient.

Unexpected

An Unexpected Adverse Event (UAE) is any Adverse Event and/or reaction, the specificity, severity, or frequency of which is not consistent with the informed consent. Further, it is not

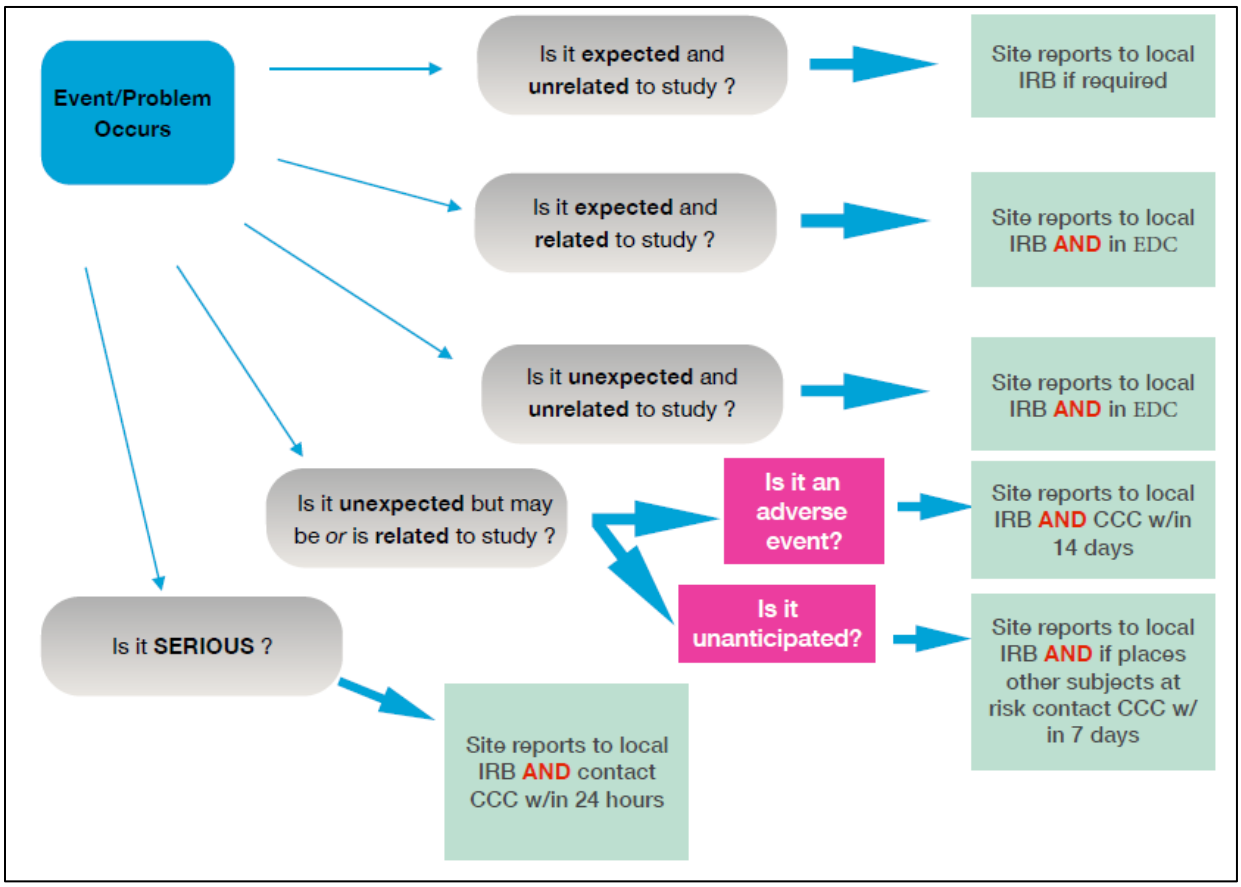
consistent with the risk information described in the general investigational plan or proposal and informed consent document on file, or is not consistent with what would be expected in a patient with critical illness.

Expected

Expected Adverse Events are those events that are included as a possible risk in the informed consent document or are expected in the course of care of a patient with critical illness.

Severity Grading

Please use the CTCAE version 4 to evaluate each adverse event and grade it as mild/moderate/severe.



Event/Problem Pathway

1. **Is it expected and unrelated to study?**
    a. **Action= Site reports to local IRB if required**
2. **Is it expected and related to study?**
    a. **Action=Site reports to local IRB AND in electronic data capture (EDC) system**

3. **Is it unexpected and unrelated to study?**
    a. **Action=Site reports to local IRB and EDC**
4. **Is it unexpected but may be or is related to study?**
    a. **Is it an adverse event?**
        i. **Action=Site reports to local IRB AND CCC within 14 days**
    b. **Is it an unanticipated adverse event?**
        i. **Action=Site reports to local IRB AND if places other subjects at risk contact CCC within 7 days**
5. **Is it SERIOUS?**
    a. **Is it likely related to the study? If so,**
        i. **Action=Site reports to local IRB AND contact CCC within 24 hours**
        ii. **Action if not related to study, enter event in the EDC tool**

All study sites are responsible for reporting their AE's and SAE's to their local IRB annually.

MACE

- A consensus of two cardiologists will adjudicate elements required to measure the occurrence of MACE (cardiac death, acute myocardial infarction, and coronary revascularization). To make these assessments, reviewers will be provided the participant's index and discharge records, follow-up call information, records obtained from follow-up, and study definitions. Records will have patient identifiers and randomization group identifiers removed. Reviewers will complete a reviewer outcome form recording the occurrence of these endpoints. Any disagreements will be settled by consensus between the two reviewers or the involvement of a third reviewer.

9. STATISTICAL ANALYSIS PLAN

The primary analysis will concentrate on the 1,200 anticipated rule-out subjects. If 12 or more (1% or more) have an MI, we shall declare the rule-out rule as unsuccessful. Secondarily, we shall look at only the three-hour subjects (eliminating the subjects classified by baseline with missing 3-hour values), anticipated to be approximately 1,000 subjects, and if fewer 1% of these have an MI (biomarker and HEART pathway), we shall secondarily declare a successful rule-out process. In short, we need either more than 99% of those called low risk to be free of MI, or more than 99% of low risk patients with Hour 3 data to be free of MIs to have a successful rule-out process.

If the true rule-out probability is 99%, there is less than a 1 in 1,000 chance of seeing 12 or more events in 1,200 subjects. The same is true using the approximately 1,000 with 3 Hour values <19 (i.e. seeing less than 12 events in 1,000 subjects).

The secondary analysis will look at prognostic factors for events in the 300 subjects not ruled out, to see if there are predictors of adverse and favorable groupings of subjects. We shall employ forward stepwise logistic regression with binary factors including gender, race (black vs. not), age (subdivided at 50 and 65), prior MI, and insurance type (private vs. not).

Modelling will continue until the residual chi-square for terms not in the model, adjusted for terms in the model have P>0.05. The analysis generates odds ratios and 95% confidence intervals for all terms in the final model, adjusted for all other terms in the model.

10. STUDY ADMINISTRATION

The investigator will conduct the trial per protocol and quality standards.

10.1 Informed Consent

Study site personnel will prepare the ICF, in compliance with Title 21 CFR Part 50, HIPAA security rules, Part 11. These documents will be submitted to the Western IRB for approval. The approved ICF will be provided to each study subject. The Investigator/designee will review the informed consent form with study subject and obtain the subject's signature. After obtaining written informed consent, the subject will enroll in the study if no exclusion criteria are present. The original copies of the ICF will be maintained by the coordinating site and the study Investigator.

10.2 Confidentiality

All samples and study records will be coded using study-specific IDs. No personal identifiers (name, address, SSN, MR#) will be shared.

This study protocol, documentation data, and all other information will be held in strict confidence by the Investigator and his or her representatives.

10.3 Monitoring Plan

All required study data will be recorded in the EDC. The data recorded is derived from study-related source documents. The coordinating site will ensure that all data on the EDC is complete and accurate and consistent with source documentation.

The designated study monitor will review the EDC for completeness and accuracy. Study data on the EDC will be verified against information on the original source document. The monitor will also check the written informed consent form (ICF), and all study-specific logs for completeness and accuracy. Protocol deviations will be recorded.

10.4 Direct access to Source Data & Study Documents

The investigator and study center will permit trial-related monitoring, audits, IRB review and regulatory inspection by providing authorized personnel from the sponsor, coordinating center, its representatives, the IRB, the FDA and other appropriate regulatory agencies direct access to all trial-related data.

Direct access is the permission to examine, analyze, verify, and reproduce any records, source documents or reports that are important to the evaluation of the study; all study records should be available for inspection and copying. Subject confidentiality will be strictly maintained.

10.5 Record Retention

All study and source documents will be maintained by the study site for a period of 2 years after the investigation is terminated or completed or for a period of 2 years after the records are no longer required or for a period greater than 2 years if required by the local institution's IRB.

10.6 Protocol Modifications

Protocol modifications are not permitted. Changes to the fundamental design or conduct of the study must be documented as a new version of the original study protocol after review and approval by the Coordinating Site. Appropriate changes are submitted to the IRB as an addendum prior to being implemented.

Statement of Investigator

I am agreeing to be an Investigator for the Roche, STOP CP clinical study to determine the clinical efficacy and performance of the Roche hs-cTnT.

I am submitting this signed statement, as a condition for providing study data to the coordinating site at the University of Florida.

I am submitting with this signed statement a summary of my education and experience (curriculum vitae).

I understand I must abide by the following conditions governing my receipt and use of the Roche STOP CP study:

a) I am required to maintain adequate records regarding the Roche STOP CP study. If the clinical/performance evaluation study is terminated, suspended, discontinued, or completed, I am to return to the coordinating site at the University of Florida any unused supplies unless other arrangements are made.
b) I understand I am to furnish my records of the STOP CP study to the coordinating site, including reports, which I agree to submit at prescribed intervals as stated in the study protocol and manual of procedures.
c) I agree to maintain records and data for a minimum period of 2 years following the date of the study.
d) Upon the request of a specifically authorized Investigator of the coordinating site or other regulatory authority, I will make records related to the STOP CP study available for inspection.
e) I agree to protect the rights, safety and welfare of the study subjects and to ensure that the regulatory requirements for obtaining informed consent are met. I agree to disclose to Roche and the coordinating site accurate financial information as required by 21 CFR Part 54.
f) I agree to disclose to Roche and the coordinating site accurate financial information as required by 21 CFR Part 54.

I agree that the Roche STOP CP study will be performed by me or under my supervision only in accordance with the Investigational Plan (protocol).

Any and all deviations from the approved protocol must have prior written approval by the coordinating site at the University of Florida. I will report all deviations from the protocol immediately.

I agree to abide by this Statement of Investigator.

Investigator Signature: _____ Date: _____

APPENDIX

1. Mahler SA, Miller CD, Hollander JE, et al. Identifying patients for early discharge: Performance of decision rules among patients with acute chest pain. INTERNATIONAL JOURNAL OF CARDIOLOGY. 2013;168(2):795-802. doi: 10.1016/j.ijcard.2012.10.010.
2. Mahler SA, Riley RF, Hiestand BC, et al. The HEART pathway randomized trial identifying emergency department patients with acute chest pain for early discharge. CIRCULATIONCARDIOVASCULAR QUALITY AND OUTCOMES. 2015;8(2):195. doi: 10.1161/CIRCOUTCOMES.114.001384.
3. Backus BE, Six AJ, Kelder JC, et al. Chest pain in the emergency room: A multicenter validation of the HEART score. Critical pathways in cardiology. 2010;9(3):164-169. doi: 10.1097/HPC.0b013e3181ec36d8.
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6. Bandstein N, Ljung R, Johansson M, Holzmann MJ. Undetectable high-sensitivity cardiac troponin T level in the emergency department and risk of myocardial infarction. JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY. 2014;63(23):2569-2577. doi: 10.1016/j.jacc.2014.03.017.
7. Reichlin T, Hochholzer W, Bassetti S, et al. Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. The New England Journal of Medicine. 2009;361(9):858-867. doi: 10.1056/NEJMoa0900428.
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