Verification of a Prediction Algorithm for Cardiopulmonary Patients Admitted to the Emergency Department

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Clinical Study Protocol

Sponsor

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List of Abbreviations

AE	Adverse Event
AVPU	Alert, Voice, Pain, Unresponsive
CABG	Coronary Artery Bypass Surgery
CKMB	Creatinine Kinase-MB
CRF	Case Report Form
eCRF	Electronic Case Report Form
ED	Emergency Department
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GCS	Glascow Coma Score
HIPAA	Health Insurance Portability and Accountability Act
HRV	Heart Rate Variability
IABP	Intra-aortic Balloon Pump
IB	Investigator's Brochure
ICU	Intensive Care Unit
IRB	Institutional Review Board
MEWS	Modified Early Warning Score
MI	Myocardial infarction
NEWS	National Early Warning Score
PCI	Percutaneous Coronary Intervention
PHI	Protected Health Information
PI	Principal Investigator
SAE	Serious Adverse Event
SpO2	Oxygen Saturation
SOP	Standard Operating Procedure
VT	Ventricular Tachycardia

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Protocol Summary

Title	Verification of a Prediction Algorithm for Cardiopulmonary Patients Admitted to the Emergency Department
Short Title	Verification of Prediction Algorithm
Study Design	Prospective observational clinical study
Study Duration	Estimated duration: 18 Months
Study Site(s)	3 Sites
Objective(s)	Verify existing prediction algorithm of cardiopulmonary events. Assess the prediction algorithm with regard to the frequency of cardiopulmonary events
Primary Analysis	Regression analysis
Number of Subjects	760 subjects
Subject Eligibility Criteria	**Inclusion Criteria** Candidates for this study must meet all of the following Inclusion criteria: 1. 18 years of age or older 2. Admission to emergency department requiring immediate medical attention due to presumed cardiac or pulmonary cause(s) and considered 2nd or 3rd tier priority in triage system. **Exclusion Criteria** Candidates will be excluded from the study if any of the following conditions are present: 1. Pregnant or suspected pregnancy 2. Significant trauma 3. Do Not Resuscitate order 4. Known as ward of the state

1 *Introduction*

1.1 *Background*

The best method by which to triage patients presenting to the emergency department (ED) has yet to be established. The key objective of the process of triage is to determine which patient is at the highest risk because that patient will require the greatest amount of resources and attention to determine the most appropriate treatment. Risk stratification is a necessary method for triaging patients, particularly in the ED, as the number of patients presenting to the ED and the availability of staff is never equally matched requiring a method to determine the order and urgency in which patients are treated.

Recent scoring systems to determine risk of significant clinical deterioration in patient health, such as the Modified Early Warning Score (MEWS), utilize vital signs (i.e., heart rate, respiration rate, blood pressure, temperature, pulse oximetry) and a subjective measure of the patient's mental status (i.e., AVPU score: alert, reacts to voice, reacts to pain, or unconscious). Elevated MEWS values has been shown to be related to mortality.[1] In the United Kingdom, a national early warning score (NEWS) has been implemented nationwide and been shown to discriminate patients at risk of the combined outcome of cardiac arrest, unanticipated intensive care unit (ICU) admission, or death within 24 hours.[2]

A novel algorithm for determining risk of acute cardiac complications, including cardiac arrest, for patients presenting to the ED has recently been reported. Unlike prior risk stratification tools that relied on basic vital sign data, this algorithm utilizes multiple metrics of heart rate variability (HRV) as well as a machine learning approach to solve the risk classification problem. The algorithm requires the collection of vital sign data, patient mental status, and *at least* 5 minutes of continuous electrocardiography (to calculate HRV metrics). It was shown to be more accurate than MEWS in predicting cardiac arrest within 72 hours of admission to hospital.[3] Furthermore, the algorithm has been used to predict serious complications (mortality, cardiac arrest, ventricular tachycardia, hypotension requiring inotropes or intra-aortic balloon pump (IABP) insertion, intubation or mechanical ventilation, complete heart block, bradycardia requiring pacing, and recurrent ischemia requiring revascularization) within 72 hours in patients presenting to the ED with chest pain. In this patient population, a score of 4 or higher from the algorithm had a sensitivity of 0.880, specificity of 0.680, positive predictive value of 0.195, and a negative predictive value of 0.985 which was better than using ST elevation/depression and troponin in predicting complications within 72 hours.[4] The primary limitation of the algorithm is that it has been developed and tested in Singaporean patients. Verification of the results of the studies using this algorithm in other patient cohorts is required. As such, the proposed study will investigate the sensitivity and specificity of the algorithm.

1.2 *Risks/Benefits*

1.2.1 Risks

This is an observational study. The only risk is a breach of the patient's protected health information.
If a patient or LAR is unwilling or unable to sign Informed Consent the data will be removed from the database and not be considered in the final analysis. These patients not participating will be replaced to ensure that the number of patients approved for this study is met.

1.2.2 Benefits

There is no benefit to an individual enrolled in this study. The benefit of this study is the verification of the algorithm.

2 Study Protocol

2.1 *Study Design*

2.1.1 Purpose

The purpose of this study is to verify an existing algorithm used to predict cardiopulmonary events in patients presenting to the emergency department.

2.1.2 Scope and Duration

This is a prospective, multi-center, observational study.

Enrollment in this study is expected to take approximately 18 months. Subjects are enrolled upon arrival to the emergency department and followed for 72 hours.

2.1.3 Sample Size

Approximately 760 subjects will be enrolled in this study.

2.1.4 Study Objectives

2.1.4.1 *Primary Objective*

The primary objective is to verify an existing prediction algorithm of cardiopulmonary events.

2.1.4.2 *Secondary Objective*

The secondary objective is to assess the prediction algorithm with regard to the frequency of cardiopulmonary events.

2.1.5 Primary Outcome Measure

2.1.5.1 *Cardiopulmonary events*

Cardiopulmonary events will be measured as the occurrence of any cardiopulmonary event, not limited to:

Cardiac arrest
Sustained ventricular tachycardia (VT)
Hypotension requiring inotropes or intra-aortic balloon pump (IABP) insertion
Intubation or mechanical ventilation
Complete heart block
Bradycardia requiring insertion of a pacing wire or external pacing, and
Percutaneous coronary intervention (PCI) or coronary artery bypass surgery (CABG),
*all within 72 hours of presentation to the ED

2.1.6 Secondary Outcomes

2.1.6.1 *Frequency of Cardiopulmonary Events*

The number of cardiac events will be measured as the occurrence of any cardiac and cardiac-related events, not limited to:

1. In-hospital Death
2. In-hospital Cardiac Arrest
3. Composite cardiovascular outcome or intervention (Lethal Arrhythmias , Acute Pulmonary Edema, Cardiogenic Shock, Myocardial Infarction, Percutaneous Coronary Intervention, Coronary artery Bypass Surgery , New or Recurrent MI, Recurrent Ischemia requiring Revascularization)

*all within 72 hours of presentation to the ED

2.1.6.2 *Cardiac Arrest*

Cardiac arrest will be defined as the event of developing ventricular fibrillation, having a sudden unexpected death, or having a resuscitation event requiring cardiopulmonary assistance (chest compressions and/or defibrillation).

2.2 *Subject Screening and Eligibility Criteria*

2.2.1 Subject Recruitment and Screening

Subjects aged 18 years or older who meet the following inclusion and exclusion criteria.

2.2.2 Inclusion Criteria

Candidates for this study must meet all of the following Inclusion criteria:

1. 18 years of age or older;
2. Admission to emergency department requiring immediate medical attention which is presumed to be cardiac or cardiopulmonary related and considered 2nd or 3rd tier priority in triage system. Symptoms including:
   Shortness of breath
   Skin pallor consistent with cardiopulmonary complications
   Chest pain
   Rapid or irregular heartbeat

   And any symptoms considered to be cardiac or cardiopulmonary-related by the investigator

2.2.3 Exclusion Criteria

Candidates will be excluded from the study if any of the following conditions are present:

1. Pregnant or suspected pregnancy;
2. Significant trauma
3. Do Not Resuscitate order
4. Known as ward of the state

2.3 *Study Procedures*

Schedule of Events			
Hospital Stay Status	**Admit**	**During**	**Discharge/ Withdrawal**
Inclusion/Exclusion Criteria	X		
Informed Consent	X[1]		
Study Evaluations			
Demographics (date of birth/age, gender and ethnicity)	X		
Smoking status	X		
ED diagnosis (primary)	X		
Final diagnosis (primary)			X
Medications including beta-blockers, combined alpha and beta-blockers, digitalis, calcium channel blocker, bronchodilators, amiodarone, other anti-arrhythmics	X	X	X

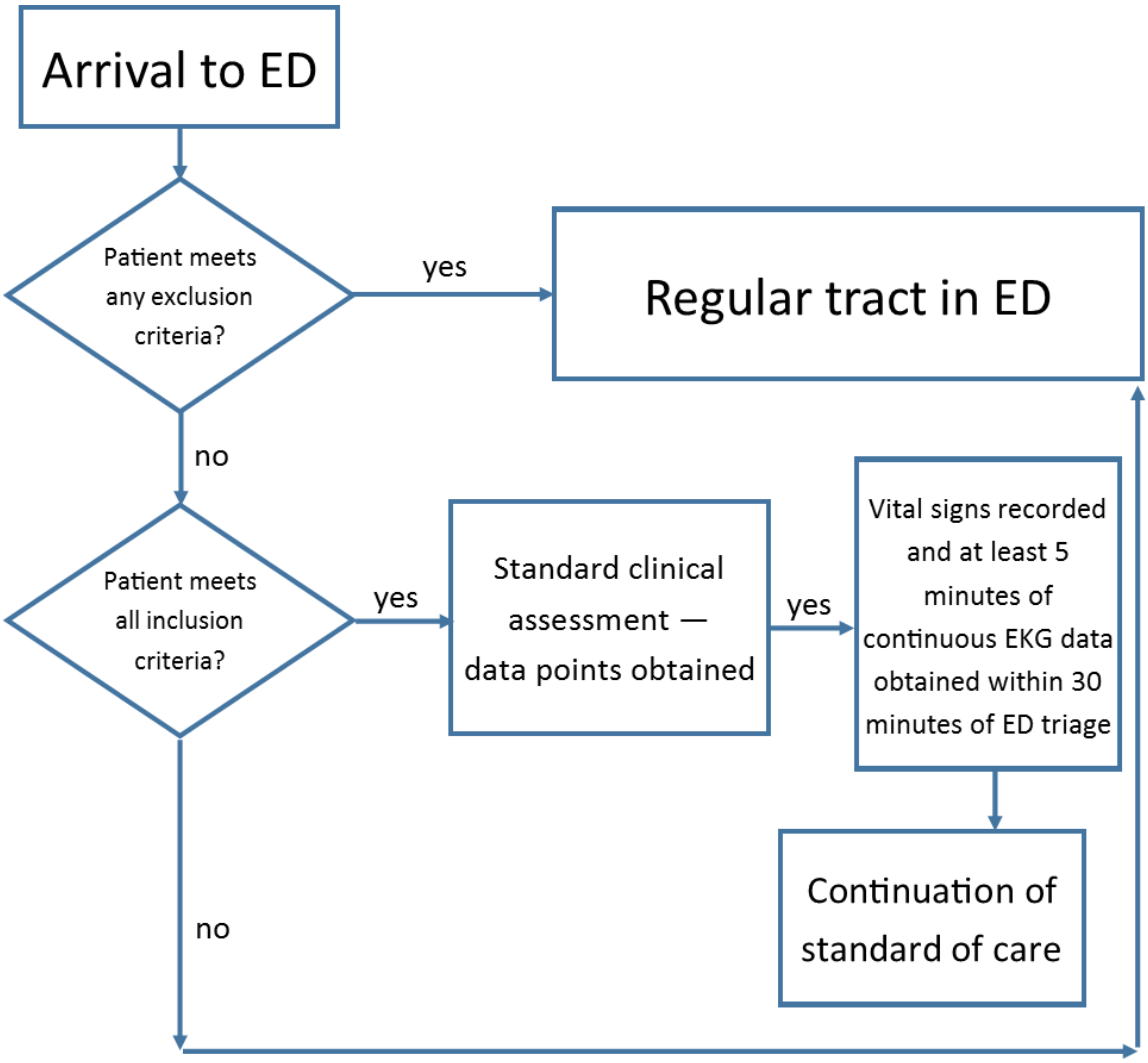
Medical history, specifically a history of ischemic heart disease, diabetes, hypertension, dyslipidemia, stroke, cancer, respiratory disease, renal disease, congestive heart disease, PCI, CABG, MI)	X		
Physical exam [redacted]	X		
Glascow Coma Score (GCS)	X		
Blood labs; specifically troponin and/or CKMB if available	X		
12-lead ECG (if patient is reporting chest pain)	X[2]		
Continuous 3-lead ECG recording of *at least* five minutes	X		
Chest Pain	X		
Symptom onset/peak within 24 hours of presentation	X		
Pain score	X		
MEWS Score	X		
Cardiopulmonary events (acute pulmonary edema, lethal arrhythmias, cardiogenic shock, myocardial infarction, percutaneous coronary intervention, coronary artery bypass surgery, recurrent ischemia requiring revascularization	X	X	X
In-hospital cardiac arrest		X	
In-hospital death		X	
Status changes (admitted to ICU, admitted to ward, etc.)		X	
Length of stay			X
Adverse Events	X	X	X

1 Every effort will be made to ensure that consent is received from the patient or patient's legally authorized representative (LAR) within 24 hours of patient enrollment. If the patient or LAR refuses consent the patient will be withdrawn from the study.
2 If applicable
3 Serious adverse events must be reported to the Sponsor within 24 hours of becoming aware of the event, but no later than 10 days after the event.

2.3.1 Subject Enrollment

Subjects are enrolled in this study when they have:

- Met all eligibility criteria.



2.3.2 Evaluation Requirements

2.3.2.1 *Assessments*

The following data points will be recorded:

- Inclusion/Exclusion Criteria
- Demographics (date of birth/age, gender and ethnicity)
- Smoking status
- ED diagnosis (primary)
- Final diagnosis (primary)
- Medications including beta-blockers, combined alpha and beta-blockers, digitalis, calcium channel blocker, bronchodilators, amiodarone, other anti-arrhythmics

- Medical history, specifically a history of ischemic heart disease, diabetes, hypertension, dyslipidemia, stroke, cancer, respiratory disease, renal disease, congestive heart disease, PCI, CABG, MI)
- Physical exam [redacted]
- 12-lead ECG (if patient is reporting chest pain)
- Continuous 3-lead ECG recording of *at least* five minutes within 30 minutes of ED triage
- Chest Pain
- Symptom onset/peak within 24 hours of presentation
- Pain score
- MEWS Score
- Cardiopulmonary events (acute pulmonary edema, lethal arrhythmias, cardiogenic shock, myocardial infarction, percutaneous coronary intervention, coronary artery bypass surgery, recurrent ischemia requiring revascularization
- In-hospital cardiac arrest
- In-hospital death
- Status changes (admitted to ICU, admitted to ward, etc.)
- Length of stay

2.3.3 Case Report Forms and Evaluations

The electronic case report form (eCRF) is the primary data collection instrument for the study. All data requested on the eCRF must be recorded. All missing data and errors must be explained by edit checks.

If a correction is required for an eCRF, the time and date stamps track the person entering or updating eCRF data and creates an electronic audit trail to reflect the reason for the change.

If the electronic data cannot be directly entered onto the eCRFs, these data should be created, imported, stored and maintained appropriately to ensure data and system security.

2.3.3.1 *Eligibility Evaluation CRFs*

The Eligibility Evaluation CRF includes the Inclusion/Exclusion Checklist.

Inclusion/Exclusion Checklist

The investigator or designee will review the inclusion and exclusion criteria. This form includes the inclusion and exclusion criteria checklist or validation.

2.3.3.2 *Protocol Deviation CRF*

This form will be used to document any protocol deviations in the study. Please see Section 2.6 and Protocol Deviation CRF for additional information regarding Protocol Deviations.

2.3.3.3 *Subject Discontinuation CRF*

This form will be used to document a subject's reason for exiting the study. Please see Section 2.5 for additional information regarding Subject Discontinuation.

2.3.3.4 *Adverse Event CRF*

All adverse events and complications will be recorded and reported on the Adverse Event CRF. Serious adverse events must be reported to the Sponsor within 24 hours, but no later than 10 days after made aware of the event.

2.4 *Classification of Adverse Events and Reporting of Adverse Events*

Serious adverse events must be reported to the Sponsor within 24 hours of becoming aware of the event, but no later than 10 days after the event. The Investigator is responsible for reporting adverse events to their individual IRBs.

Serious adverse event is defined as:

- Death
- A serious deterioration in the health of the patient that results in a life-threatening illness or injury
- A permanent impairment of a body structure of body function
- In-patient hospitalization or prolongation of existing hospitalization
- Medical or surgical intervention to prevent permanent impairment to body structure or function
- Fetal distress, fetal death or congenital abnormality or birth defect.

2.4.1 Adverse Event Reporting

Adverse event reporting will comply with the regulations of the local IRB.

2.5 *Subject Withdrawal*

An enrolled subject is considered 'withdrawn' from the study if their participation in the study is discontinued for any reason after enrollment. Possible reasons for withdrawal include:

- Eligibility Criteria not met
- Investigator judgment

If a subject withdraws from the study, a Subject Discontinuation CRF will be completed.

2.6 *Protocol Deviations*

An Investigator shall notify the sponsor and reviewing IRB of any deviations from the study protocol that are done to protect the life or physical well-being of a subject. Such notice shall be given as soon as possible, but no later than 5 working days after the deviation occurred.

A protocol deviation is defined as a deviation from the study protocol.

Protocol deviations will be documented on a Protocol Deviation CRF.

3 Statistical Analysis

3.1 *Introduction*

The primary objective is to verify an existing prediction algorithm of cardiopulmonary events. The secondary objective is to assess the prediction algorithm with regard to the frequency of cardiopulmonary events.

Standard summary statistics will be calculated for relevant study variables. For continuous variables, summary statistics will include means, medians, standard deviations and 95% confidence intervals around the means. Categorical variables will be summarized using counts and percentages. Statistical analyses will be conducted in SAS version 9.1 or above (SAS Institute, Cary, N.C.) or another statistical analysis package.

3.2 *Primary Outcome Measure*

The primary outcome measure is the occurrence of cardiopulmonary events. It will be measured as the occurrence of any cardiopulmonary event, within 72 hours of presentation to the ED, including:

Cardiac arrest
Sustained ventricular tachycardia (VT)
Hypotension requiring inotropes or intraaortic balloon pump (IABP) insertion
Intubation or mechanical ventilation
Complete heart block
Bradycardia requiring insertion of a pacing wire or external pacing, and
Percutaneous coronary intervention (PCI) or coronary artery bypass surgery (CABG).

For the primary outcome measure of occurrence of cardiopulmonary events, binary logistic regression will be used to estimate the probability that a cardiopulmonary

event has occurred given the values of explanatory variables, given by the following equation:

- Y is the primary outcome measure
  Y_i = 1 if a cardiopulmonary event has occurred
  Y_i = 0 if there is no cardiopulmonary event
- π_i = the probability of a cardiopulmonary event
- $X = (X_1, X_2, ..., X_k)$ being the set of explanatory variables

Model:

$$\text{logit}(\pi_i)=\beta_0+\beta_{1xi1}+\ldots+\beta_{kxik}$$

A Receiver Operating Characteristic Curve will be constructed and the area under the curve will be calculated to assess the model sensitivity.

3.3 *Secondary Outcome Measure*

The secondary outcome measure of the frequency of any cardiac event will be measured as the occurrence of any cardiac and cardiac-related events, not limited to:

1. In-hospital Death
2. In-hospital Cardiac Arrest
3. Composite cardiovascular outcome or intervention (Lethal Arrhythmias , Acute Pulmonary Edema, Cardiogenic Shock, Myocardial Infarction, Percutaneous Coronary Intervention, Coronary artery Bypass Surgery , New or Recurrent MI, Recurrent Ischemia requiring Revascularization)

For the secondary outcome measure of frequency of any cardiopulmonary event, multiple linear regression will be used to estimate the probability that an increase in the number of cardiopulmonary events given the values of explanatory variables, given by the following equation:

- Y_i is the number of cardiopulmonary events
- π_i = the probability of a cardiopulmonary event
- $X = (X_1, X_2, ..., Xi)$ be the set of explanatory variables
- p=number of β coefficients in the model (including the intercept)

Model:

$$y_i=\beta_0+\beta_{1xi,1}+\beta_{p-1xi,p-1}+\epsilon i$$

3.4 *Randomization*

This study is observational and no randomization of subjects will occur.

3.5 *Blinding*

This study is observational and no blinding will occur.

3.6 *Missing Data*

The primary analysis will be based on the data as observed. Two additional sensitivity analyses will be performed where subjects with missing data are (1) assumed to have no cardiopulmonary events and (2) assumed to have a cardiopulmonary event.

3.7 *Sample Size*

Approximately 760 subjects are planned to be enrolled in the study to provide 634 subjects in the final analysis.

When the sample size is 634, the logistic regression test of β=0 (α = 0.050 two-sided) will have 80% power to detect a β of 0.747 (an odds ratio of 2.111); this assumes that one normally distributed covariate x is being added to the model after adjustment for prior covariates, that its multiple correlation with covariates already in the model is 0.500 and, that the proportion of successes at the mean of x is 0.050.

4 Monitoring Procedures

4.1 *Monitoring*

This study will be monitored according to appropriate regulations and SOPs. The Investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor is given access to all the study-related documents and related facilities, and has adequate space to conduct the monitoring visit.

4.2 *Investigator/Site Selection*

The following documents must be received prior to site initiation and maintained at the site and Sponsor:

- Signed Clinical Study Agreement;
- Current Medical License;
- Current Curriculum Vitae (CV) for Primary Investigator(s) – dated and signed

- IRB/EC Approval Letter; and
- IRB Membership List and/or Accreditation Statement

Additional items that may be collected, are preferably collected prior to initiation, but not required at that time:

- CV's for Co-Investigator(s) – dated and signed; and
- Site Personnel Training Record(s).

4.3 *Case Report Form Review*

A database that is compliant with 21 CFR Part 11 will be used. eCRFs received from the site will be documented with their date of receipt and entered into the study database. If there is missing, incomplete, unclear or discrepant information recorded on eCRFs, a Data Clarification Form (DCF) will be generated. The DCF will be sent to the Investigator for completion and signed by the appropriate site personnel. The DCF will then be sent back to the Sponsor to update the database. All common modules are demographics, screening, adverse events, labs, medical history, medications, procedures, treatment discontinuation, study completion, and signatures.

4.4 *Source Documents*

Source data is all information, original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Examples of source data include: Patient Medical Records, recorded data from automated instruments, and subject files involved in the clinical study.

4.5 *Interim On-site Monitoring*

The monitor will maintain personal contact with the Investigator and staff by fax, phone, mail, and on-site visits. The monitor will require access to all subjects' records at each site visit. These may include:

- Patient Medical Records
- Investigator Administrative Records
- Subject Binders

Monitoring will verify:

- Protocol and regulatory compliance;
- Verification of data recorded on Case Report Forms to source documents; and
- Adequate subject enrollment.

4.6 *Final Monitoring Visit*

At the close of the study, the monitor will make a final on-site visit. The purpose of this visit is to:

- Collect all outstanding study data;

- Insure that the Investigator's files are accurate and complete;
- Review record retention requirements with the Investigator;
- Assure that all requirements are met for the closure of the study.

5 Study Administration

5.1 *Study Sponsor*

ZOLL Medical is the study sponsor and responsible for selecting qualified Investigators and providing them with the information they need to conduct the study properly, ensuring proper monitoring of the clinical site, ensuring that IRB review and approval are obtained, and ensuring that any reviewing IRBs are promptly informed of significant new information about the study.

5.2 *Applicable Regulations*

The following regulations were considered in developing/designing this study and apply to the ongoing conduct of the study:

- ISO 14155

5.2.1 Institutional Review Board

Prior to participating in the study, the Investigator must forward written approval from the appropriate reviewing IRB. The Investigator is responsible for obtaining and maintaining IRB approval to participate in this study and forwarding evidence of IRB notification of approval, disapproval, or study termination to Sponsor.

5.2.2 Informed Consent

Patients will typically be unable to give informed consent at the time of enrollment based on the seriousness of their injuries or the process in which medical care is given. As this is an observational study and the data collected is only that of standard of care treatment this trial should be considered non-significant risk. Every effort will be made to ensure that consent is received from the patient or patient's legally authorized representative (LAR) within 24 hours of patient enrollment.
If a patient or LAR is unwilling or unable to sign Informed Consent the data will be removed from the database and not be considered in the final analysis. These patients not participating will be replaced to ensure that the number of patients approved for this study is met.

Records and Reports

5.2.3 Investigator Records

The Investigator is responsible for the preparation (review and signature) and retention of the records cited below. Records are subject to inspection and must be retained for a period of at least two (2) years (or according to local regulatory requirements) after the study is terminated or the date that the records are no longer required for purposes of supporting publications. Records to be maintained by the Investigator include:

- Study protocol and all amendments
- Signed Clinical Study Agreement
- IRB approval letter, including informed consent
- IRB membership list
- Correspondence relating to the study
- CVs for all Investigators
- Site personnel signature list
- Clinical monitor sign-in log
- Blank set of CRFs and instructions for completion
- Patient enrollment log
- Reports (includes annual reports, final reports from Investigator and Sponsor)

The following records must be maintained for each subject enrolled in the study:

- All data entered (e)CRF's
- Supporting documentation of any complications

ZOLL reserves the right to secure data clarification and additional medical documentation on subjects enrolled in this study.

5.2.4 Sponsor Records

ZOLL Medical will maintain the following accurate, complete, and current records that are cited below.

5.2.4.1 *Sponsor Administrative Records*

- Enrolled Subject Identification Log
- Site Training and Monitoring Log
- Device Accountability Records
- Non-Disclosure Agreement
- Clinical Trial Agreement
- Investigator Information
    - Current CV(s)
    - Current Medical License
    - Financial Disclosure Forms(s)
- Monitoring
    - Monitoring Letter(s)
    - Monitoring Visit Report(s)
    - Site Visit Report(s)
    - Site Personnel Training Record(s)
- IRB
    - IRB roster or letter of assurance
    - IRB Approval Letter(s)

- All study conduct related correspondence with an IRB or FDA
- All study conduct correspondence with Site
- Required reports (reference Table 5)
- Documents Received Tracking Log
- Study protocol and previous revisions

5.2.4.2 *Subject Records*

- Original completed CRFs
- Copies of all completed logs and other subject specific forms (originals are maintained at site until the end of the study)
- Original subject specific protocol deviations
- Adverse event supporting data (e.g. EMS reports, medical records)
- Original completed Data Clarification Forms (DCFs)

5.3 *Publications*

All publications and strategy will be reviewed and approved by the Sponsor. In general, publications using study data will be managed as follows:

Authorship Selection
Authors will be selected based on the following criteria:

- Investigator's participation in the study design process; or
- Investigators participation in the study analysis process; and
- Providing substantive contributions to the writing and development of the resulting publication.

Confidentiality
The Sponsor and authors will assure that no information, which would reveal a subject's identity, is used in any publication. Information, which could be used to establish a subject's identity, should not be provided to the Sponsor. Authors and the Sponsor will take every reasonable precaution to protect the identity of subjects enrolled in the study.

Review of Communication Guidelines
Investigators will receive a communication regarding the authorship selection, the publication co-authors and to which scientific platform the publication will be submitted.

5.4 *Study Discontinuation*

Sponsor will notify the Investigator of the completion or termination of the study or of the Investigator's participation in the study. The Sponsor will provide a summary to the reviewing IRB of the study within 6 months of study termination.

5.5 *Use of Study Findings*

5.5.1 Subject Confidentiality

In conducting the study, the investigational site will comply with all applicable laws and regulations relating to the confidentiality and security of individually identifiable medical information including but not limited to the requirements of the Health Insurance Portability and Accountability Act (HIPAA).

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

All personal information pertaining to subjects will be kept confidential. Subjects will be identified only by their Subject ID Number. Clinical study documents and hospital and clinic medical records pertaining to subjects may be reviewed by Sponsor personnel or their representatives.

Information obtained in the course of executing this study, including still and motion photography, may be presented for regulatory, clinical or educational purposes as long as no subject is identified.

5.5.2 Ownership of Study Data

The cumulative set of data collected by ZOLL Medical from the Investigator is considered ZOLL's data.

6 Appendices

ECG Monitoring

The X Series is intended for use to monitor and/or record 3-, 5-, or 12-lead ECG waveform and heart rate, and to alarm when heart rate is above or below limits set by the operator.

Each site will receive 3 X-series monitors to be used on subjects enrolled in the study. These devices will be on loan and will be returned to the sponsor at the completion of the study.

The patient's ECG is monitored by connecting the patient to the unit via a 3-, 5-, or 12-lead patient cable or hands-free therapy electrodes. The ECG waveform is presented on the display along with the following information:

• averaged heart rate, derived by measuring R to R intervals

• lead selection - I, II, III, aVR, aVL, aVF, V1, V2, V3, V4, V5, V6 (with ECG cable), PADDLES, or PADS.

• ECG size - 0.125, 0.25, 0.50, 1.0, 2.0, 4.0 cm/mV, AUTO

• status messages

The ECG bandwidth is user selectable.

IMPORTANT: FOR PURPOSES OF THIS STUDY WE ARE REQUIRING THE RECORDING OF A 3-LEAD, CONTINUOUS ECG OF AT LEAST 5 MINUTES.

Continuous Waveform Recording

Continuous waveform recording allows you to record continuous waveforms to a full disclosure case log for the patient being monitored. This feature needs to be enabled by a supervisor. The supervisor can access this feature by pressing the Setup quick access key ( ), and then selecting Supervisor>Log>Waveform Recording. In this menu, the following settings can be customized:

• Record Displayed Waveforms – Record only the top waveform that is displayed or record all waveforms that are displayed.

• Record Additional Waveforms – Always record the CO2 waveform or always record the IBP and the CO2 waveforms.

Note: When Continuous waveform recording is disabled, no waveforms (except snapshots) are recorded.

The full disclosure case can, at a minimum, concurrently store the following information:

- 32 monitor snapshots
- 500 non-ECG events
- 24 hours of continuous ECG (4 waveforms), Capnography, IBP (3 channels), and Pads Impedance

The actual information that is stored depends on usage. Also, the specific combination of stored continuous waveform data depends on how the waveform recording settings are configured in the Supervisor menu.

ECG Monitoring Setup

The proper application and placement of electrodes is essential for high quality ECG monitoring. Good contact between the electrode and skin minimizes motion artifact and signal interference.

The following procedure describes how to monitor a patient’s ECG using 3- and 5-Lead ECG cables.

To monitor a patient’s ECG using 3- and 5-Lead ECG cables, perform the following steps:

1. Prepare the patient's skin for electrode application:
2. Apply the electrode pads to the patient.
3. Connect each lead of the ECG cable to the appropriate electrode.
4. Insert the patient cable plug into the ECG input connector on the X Series unit.
5. Select the ECG waveforms to be displayed on the waveform trace display screen.
6. Observe the patient‘s electrocardiogram on the display, and adjust size of the ECG waveform trace, as necessary.

Preparing the Patient for Electrode Application

The proper application of electrodes is essential for high quality ECG monitoring. Good contact between the electrode and skin minimizes motion artifact and signal interference.

Before applying electrodes, prepare the patient’s skin, as necessary:

- Shave or clip excess hair at electrode site.
- Clean oily skin with an alcohol pad.
- Rub site briskly to dry.

Applying Electrodes to the Patient

The following sections show where to place electrodes when using 3- and 5-Lead cables to perform ECG monitoring. For 3-Lead ECG cables, apply electrodes as in Figure 4-1, 3-Lead Electrode Placement. For 5-Lead ECG cables, apply electrodes as in Figure 4-2, 5-Lead Electrode Placement.

Avoid placing electrodes over tendons and major muscle masses.

Make sure that the ECG electrodes are placed to allow defibrillation, if necessary.

3-Lead Electrode Placement

Depending upon local usage, the ECG leads are marked either RA, LA, and LL (or R, L, and F). The following table shows the markings and color codes for the different lead sets.

AHA Color Coding	IEC Color Coding	Placement of Electrodes
RA/White Electrode	R/Red Electrode	Place near patient's right mid-clavicular line, directly below clavicle
LA/Black Electrode	L/Yellow Electrode	Place near patient's left mid-clavicular line, directly below clavicle.
LL/Red Electrode	F/Green Electrode	Place between 6th and 7th intercostal space on patient's left mid-clavicular line.

[redacted]

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7 References

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