Acute Coronary Syndrome Quality Improvement in Kerala (ACS QUIK)
Cluster Randomized, Stepped Wedge Clinical Trial

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TABLE OF CONTENTS

LIST OF ABBREVIATIONS

ACS	Acute Coronary Syndrome
AE	Adverse Event
CHD	Coronary Heart Disease
CVD	Cardiovascular Disease
LMIC	Low- and Middle- Income Countries
MACE	Major Adverse Cardiovascular Event
SAE	Serious Adverse Events
SAQ	Seattle Angina Questionnaire
WHO	World Health Organization

STUDY SCHEMA

This study is a cluster randomized, stepped wedge clinical trial assessing implementation and effect of a locally-developed quality improvement toolkit for patients admitted with acute coronary syndrome (ACS) in Kerala, India. Hospitals will be randomized after stratification for size to one of five steps. After a four-month baseline period, the quality improvement toolkit will be implemented in a random subset of hospitals in step 1 (cohort 1). Through a one-way crossover design, these hospitals will continue to use the quality improvement toolkit through the end of the trial for all acute coronary syndrome (ACS) patients. Cohorts 2 through 5 will implement the quality improvement toolkit every 4 months at months 8, 12, 16 and 20, continuing the use of the toolkits from that time forward to the end of the study. The primary outcome is 30-day major adverse cardiovascular events (MACE) rates. Rates will be continuously collected and compared at one interim time point for safety and efficacy. Final analysis compares MACE rates before and after implementation of the quality improvement toolkits, accounting for cluster effects of hospital, cohort, and time.

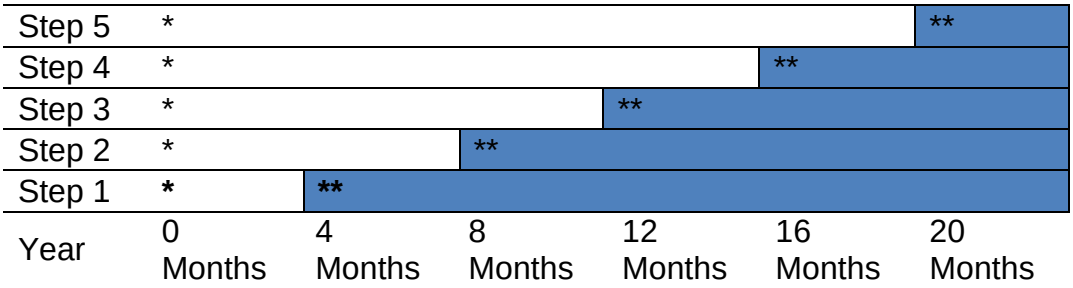


Figure 1. Stepped Wedge Design
*Denotes randomization at beginning of the study to cohort group, n = 12-14 hospitals per cohort.
** Denotes progression from usual care to intervention by locally-developed quality improvement toolkits.

STUDY SUMMARY

Title	Acute Coronary Syndrome Quality Improvement in Kerala
Short Title	ACS QUIK
Protocol Number	Version 22 September 2014
Phase	3
Methodology	Cluster Randomized Stepped Wedge
Study Duration	2 Years
Study Center(s)	Multicenter: 60-70 clinics/hospitals in Kerala, India
Objectives	Develop, implement and evaluate the effect of a quality improvement toolkit on 30-day MACE rates in ACS patients
Number of Subjects	15,750

Diagnosis and Main Inclusion Criteria	Hospitalization due to ACS
Study Product(s), Dose, Route, Regimen	Locally-Developed Quality Improvement Toolkit
Duration of administration	During in-hospital care for Acute Coronary Syndrome
Reference therapy	Usual Care
Statistical Methodology	30-day MACE rates are compared before and after implementation of a quality improvement toolkit. Analysis includes cluster effects of hospitals, cohorts and time.

1.0 BACKGROUND AND RATIONALE

1.1 Disease Background

Cardiovascular disease (CVD) is the leading cause of death worldwide with 80% of deaths occurring in low- and middle-income countries (LMIC).[1] In India, a World Bank LMIC, coronary heart disease (CHD) causes 40% of deaths in urban areas and 30% of deaths in rural areas.[2] CHD prevalence in India has increased with a recent study estimating that 30 million individuals in India have CHD.

In addition to increased prevalence, the burden of CVD in India may be higher than in developed and other developing countries due to differences in age-standardized death rates. WHO reported 2004 age-standardized CVD death rates for all ages are 174.7 per 100,000 in Britain, 178.8 per 100,000 in United States, 279.5 per 100,000 in China, and 381.5 per 100,000 in India.[3] Increased burden at a younger age leads to loss of productivity, depleted economic growth and increased social challenges.[4] The World Health Organization (WHO) proposes a three-pronged approach to curtailing global trends in CVD; surveillance and monitoring, reduction of risk factors, and improved management and healthcare through early detection and timely treatment.

1.2 Study Agent(s)/Devices Background and Associated Known Toxicities

Studies demonstrating improved outcomes with use of guideline-based therapies in high-income countries have demonstrated improvements in clinical outcomes in ACS patients.[5-9] Similar large-scale studies have not been carried out in India, although pilot investigation shows a potential benefit of implementation of education and standardized health system interventions.[10]

1.3 Rationale

System-level quality improvement initiatives in ACS, while successful in high-income countries, have not been extensively evaluated in LMIC, yet could be sources of innovation in the field of cardiovascular implementation science.

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

2.1.1 Compared with usual care, to evaluate the effect of a locally-developed, evidence-based health care quality improvement toolkit

on 30-day major adverse cardiovascular events (MACE) in patients admitted with acute coronary syndrome.

2.2 Secondary Objectives

2.2.1 To evaluate health related quality of life in post-ACS patients (30-days) using a translated and validated version of the Seattle Angina Questionnaire (SAQ).

2.2.2 To evaluate individual- and household-level impoverishing effects of an ACS event in the context of the recent implementation of a national government insurance program for families below the poverty line.

2.2.3 Compared with usual care, to evaluate the effect of a locally-developed, evidence-based health care quality improvement toolkit on in-hospital and discharge medication prescription rates, discharge advice relative to healthy lifestyles, and in-hospital and 30-day expanded MACE.

2.2.4 To evaluate the association between concordance with locally-defined performance measures for ACS care and in-hospital and 30-day MACE.

2.3 Endpoints

Composite of 30-daymajor adverse event rate, defined as death, myocardial infarction, stroke, and major bleeding defined by GUSTO criteria.

3.0 PATIENT ELIGIBILITY

Subjects must meet all of the inclusion and exclusion criteria to be registered to the study. Study treatment may not begin until a subject is registered.

3.1 Inclusion Criteria

All hospitals which previously participated in the Kerala ACS Registry will be eligible for participation in this study. These hospitals include urban, semi-urban and rural locations and are representative of the region. All patients who present with ST segment elevation myocardial infarction or non-ST segment elevation myocardial infarction will be eligible to consent and participate in the study if:

3.1.1 The Hospital has agreed to participate in the trial, including randomization.

3.1.2 Subjects must have the ability to understand and the willingness to sign a written informed consent.

3.1.3 Subjects must be aged 18 years or older to participate in the trial.

3.2 Exclusion Criteria

Patients who do not require ACS care at the participating hospital will not be eligible to participate in the study.

4.0 TREATMENT PLAN

4.1 Treatment Dosage and Administration

4.1.1 Quality Improvement Toolkits

Quality improvement toolkits for ACS patients (clinical standards, guidelines, pathways, electronic audit-feedback, and cardiac arrest code teams) will be developed through workshops with providers from the Kerala ACS registry.

Toolkits will be implemented at each step in randomly selected cohorts of hospitals, according to the stepped wedge design (five steps planned over two years). At a minimum, toolkits will include locally-developed standard admission and discharge order sets, poster-size clinical pathways and algorithms, standardized patient lifestyle counseling advice, and electronic audit-feedback systems.

At baseline, all Hospitals will provide ACS care per normal procedures for no shorter than a period of 4 months. At 4 months, one cohort will randomly be selected through randomization stratified by hospital size. This step will implement the quality improvement toolkit and continue the use of the toolkit through the end of the trial (2 years). Additional cohorts will be sequentially randomized at months 8, 12, 16, and 20.

Patients presenting at participating hospitals will be treated per the ACS care and procedures in place at the hospital at the time of presentation. Patients will be followed up at 30-days either by telephone or in-person visit to determine the occurrence of any major adverse cardiovascular events.

4.1.2 Seattle Angina Questionnaire & Micro-Economic Assessment

A 2,200 subset of patients will also be asked to complete the Seattle Angina Questionnaire and a Micro-Economic Assessment.

Completion of these additional questionnaires necessitates an in-person visit.

4.2 Concomitant Medications/Treatments: None

4.3 Other Modalities or Procedures: None

4.4 Duration of Therapy

Patients will be administered care for ACS upon presentation to the hospital. ACS care will be provided per the hospital care guidelines, either standard of care or standard of care with the quality improvement toolkit. After provision of informed consent, data will be collected during hospitalization and through 30 days. Patients may decide to withdraw from the study at any point.

4.5 Duration of Follow Up

Patients will be followed-up 30 days post hospitalization at which time they will be contacted to provide information related to MACE and secondary aims. Some patients may also be contacted to complete the Seattle Angina Questionnaire or a micro-economic assessment.

4.6 Removal of Patients from Protocol Therapy

Patients will be removed from therapy when any of the criteria listed in Section 5.5 apply. Notify the Principal Investigator, and document the reason for study removal and the date the patient was removed in the Case Report Form or Electronic Database. The patient should be followed-up per protocol.

4.7 Patient Replacement

Removal or loss to follow up of a patient does not require a replacement patient to be enrolled. Best effort shall be made to inform all eligible patients presenting with ST segment elevation myocardial infarction or non-ST segment elevation myocardial infarction of the ACS QUIK trial and proceed with the informed consent process. No maximum number of participants is specified for any single hospital.

5.0 STUDY PROCEDURES

5.1 Screening/Baseline Procedures

Patients will be assessed and admitted per local hospital procedures, either standard of care or standard of care plus quality improvement toolkit. Patients determined to require care for ST segment elevation myocardial infarction or non-ST segment elevation myocardial infarction will be invited to participate in the trial through the informed consent process.

All procedures and local hospital data capture required for ST segment elevation myocardial infarction or non-ST segment elevation myocardial infarction care will be performed regardless of enrollment in the ACS QUIK trial. In-hospital data collection will not require informed consent as permitted through the Common Rule. Follow-up data collection will require informed consent.

5.1.1 Informed Consent

Informed consent will be obtained from each participant per guidelines for ethical research in human subjects. IRB or Ethics Committee oversight is provided by each hospital or through the Ethics Committee of the Cardiological Society of India, Kerala Chapter. Northwestern University IRB approval has also been obtained for this study.

5.1.2 Screening/Baseline Data

All data will be recorded by the enrolling hospital. Data will be entered as applicable to local systems and/or the ACS QUIK electronic database after informed consent is provided. Screening and baseline data may include but is not limited to:

5.1.2.1 Medical History

5.1.2.2 Demographics

5.1.2.3 Previous and concomitant medications

5.1.2.4 Physical Exam and Vital Signs

5.1.2.5 Performance Status

5.1.2.6 Adverse event assessment

5.1.2.7 Hematology

5.1.2.8 Serum Chemistries

5.2 Procedures During Treatment

Treatment will be administered per local hospital procedure, either standard of care or standard of care plus Quality Improvement Toolkit. Where a patient is enrolled in the ACS QUIK trial, all patient data will be recorded in the ACS QUIK electronic database in addition to local hospital databases (per hospital procedure). Data entry in the electronic database will occur within 7 days of patient discharge for in-hospital data collection,

and within 48 hours of patient contact for 30-day follow-up, Seattle Angina, and Micro-Economic assessments.

5.2.1 Admission

Upon admission to the hospital, patients will be assessed for ST segment elevation myocardial infarction or non-ST segment elevation myocardial infarction according to treatment program at use in the hospital at time of presentation with symptoms. Where the quality improvement toolkit is in place, standard admission sets will be used.

5.2.2 Treatment

Patients will be treated for ST segment elevation myocardial infarction or non-ST segment elevation myocardial infarction according to the treatment program at use in the hospital at the time of enrollment of the patient in the study. Where the quality improvement toolkit is in place at the time of enrollment, standardized clinical pathways will be used during treatment.

5.2.3 Discharge

Patients will be discharged according to the treatment program at use in the hospital at the time of enrollment of the patient in the study. Where the quality improvement toolkit is in place at the time of enrollment, standardized discharge sets will be used.

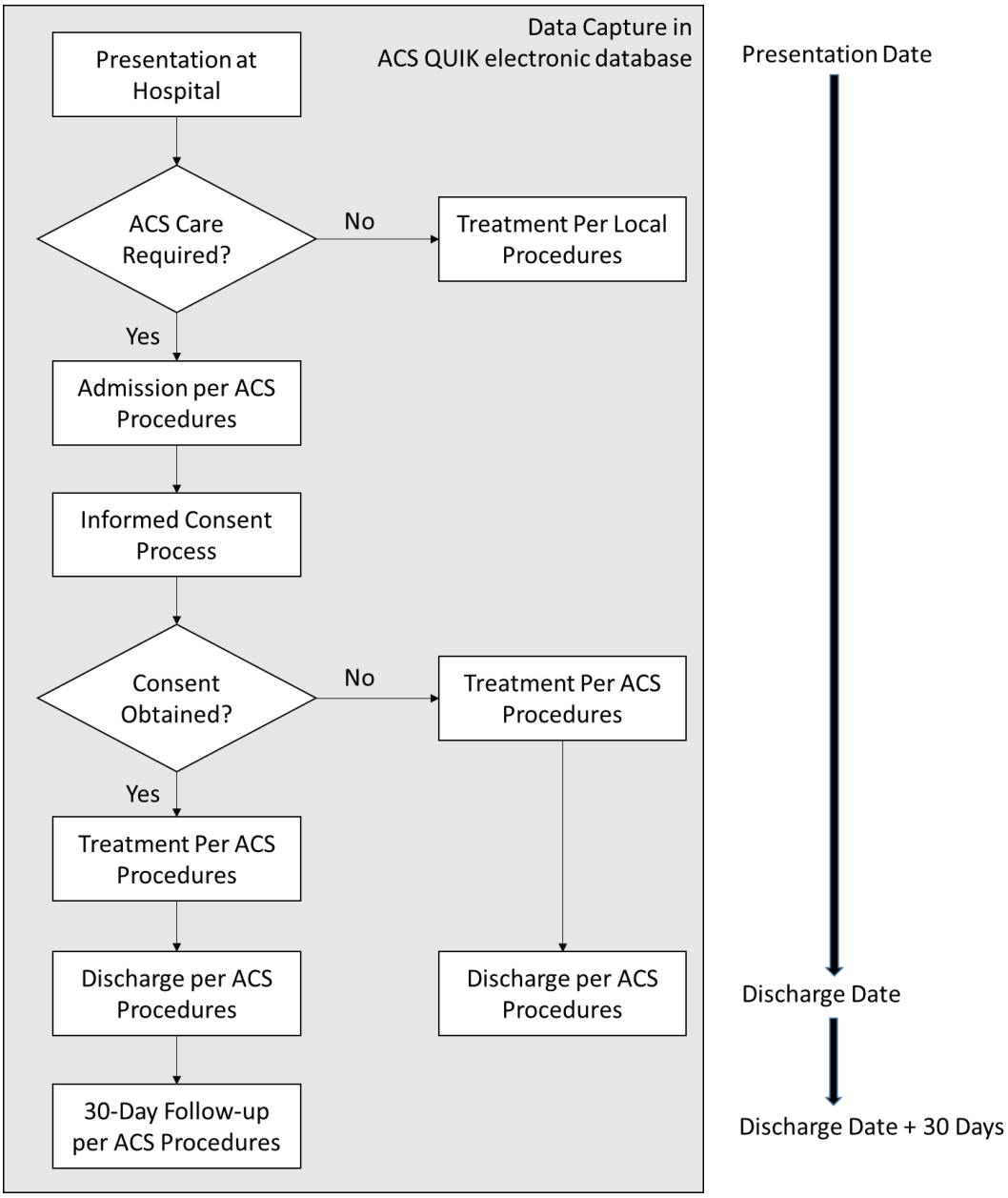
5.2.4 30 Days after Hospitalization

Patients will be contacted at 30-days post hospitalization. Contact may be by telephone, home visit or office visit as applicable to collect information on vital status, re-hospitalization, and adverse events. Some patients will also be asked to complete the Seattle Angina Questionnaire and a micro-economic assessment.

5.3 Follow-up Procedures

Patients will be followed up at 30 days post hospitalization as described above. Patients will not be followed further than 30 days post hospitalization.

5.4 Time and Events



5.5 Removal of Subjects from Study

Patients may be removed from the study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation will be documented and may include:

5.5.1 Patient voluntarily withdraws from treatment (follow-up permitted);

5.5.2 Patient withdraws consent (termination of treatment and follow-up);

5.5.3 Patient is unable to comply with protocol requirements;

5.5.4 Treating physician judges continuation on the study would not be in the patient's best interest;

5.5.5 Lost to follow-up. If a research subject cannot be located at 30 days post hospitalization, the subject may be considered "lost to follow-up." All attempts to contact the subject at 30 days must be documented and approved by the Data Monitoring Committee as outlined in the Data Management Plan.

6.0 ADVERSE EVENTS

6.1 Adverse Event Monitoring

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of Subjects enrolled in the studies as well as those who will enroll in future studies using similar agents.

6.2 Definitions

6.2.1 Adverse Event (AE):

Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An adverse event (also referred to as an adverse experience) can also be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An adverse event can arise from any use of a drug (e.g., off label use, use in combination with another drug) and from any route of administration, formulation or dose, including overdose.

6.2.2 Serious Adverse Event (SAE):

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death,
- a life-threatening adverse reaction,
- inpatient hospitalization or prolongation of existing hospitalization,
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions,
- or a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

6.2.3 Expected Adverse Event

This study assesses the effect of a quality improvement toolkit on 30-day major adverse cardiovascular event (MACE) rates defined as one or more of the following:

- Death
- Myocardial infarction
- Stroke
- Major bleeding defined by GUSTO criteria

These adverse events are expected as inherent to the trial.

6.2.4 Unanticipated Adverse Event (uAE)

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, of an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. "Unexpected" as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

6.3 Reporting Requirements for Adverse Events

6.3.1 Routine Reporting

All SAEs and AEs will be routinely captured through the electronic data capture form and reported semi-annually and at the interim safety analysis.

6.3.2 Expedited Reporting

In addition to routine reporting, the Principal Investigator and site Principal Investigator must be notified within 24 hours of learning of any unanticipated SAEs, regardless of attribution, occurring during the study or within 30 days of treatment. Unanticipated SAEs are reported within 10 business days to institutional officials.

Unanticipated SAEs are followed to resolution or stabilization, and any follow-up information for an unanticipated SAE is reported

within the same timelines as the original SAE. If the investigator becomes aware of an unanticipated SAE occurring within 15 days of patient withdrawal from the study intervention, it is immediately reported to the CCDC and site IRB.

6.3.3 Additional Reporting

In addition to adverse event reporting, the institutional officials must be notified within 10 business days of “any unanticipated problems involving risk to subjects or others” (UPR/UPIRSO).

The following events meet the definition of UPR:

1. Any serious event (injuries, side effects, deaths or other problems), which in the opinion of the Principal Investigator was unanticipated, involved risk to subjects or others, and was possibly related to the research procedures.
2. Any serious accidental or unintentional change to the IRB-approved protocol that alters the level of risk.
3. Any deviation from the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research subject.
4. Any new information (e.g., publication, safety monitoring report, or updated sponsor safety report), interim result or other finding that indicates an unexpected change to the risk/benefit ratio for the research.
5. Any breach in confidentiality that may involve risk to the subject or others.
6. Any complaint of a subject that indicates an unanticipated risk or that cannot be resolved by the Principal Investigator.

6.4 Stopping Rules

Data safety monitoring board (DSMB) will provide recommendation after one interim data analysis at one-year to stop the trial based on review of safety and efficacy data. Discontinuation of the study may be determined by recommendation of the DSMB. Hospitals will be encouraged to remain in the study through completion unless otherwise recommended by interim analysis.

7.0 INTERVENTION INFORMATION

7.1 Description of Quality Improvement Toolkit

The quality improvement toolkit is developed from focus group discussions with clinicians and care providers in the Kerala ACS registry. The quality improvement toolkit is implemented on a hospital wide basis. The toolkit will include provider education materials, standardized admission sets,

clinical pathways and standardized discharge sets. The toolkit will additionally include an audit and feedback mechanism through the ACS QUIK electronic database.

8.0 STATISTICAL CONSIDERATIONS

8.1 Study Design/Study Endpoints

Study design and endpoints are covered in detail within the ACS QUIK Statistical Analysis Plan (Version 22 September 2014).

As described in the ACS QUIK SAP, the primary endpoint is “Composite of 30-day major adverse event rate, defined as all-cause death, myocardial infarction, stroke, and major bleeding defined by GUSTO criteria (intracerebral hemorrhage or bleeding resulting in substantial hemodynamic compromise requiring treatment (GUSTO Investigators. *N Engl J Med* 1993; 329:673-682))”.

As described in the ACS QUIK SAP, secondary endpoints include “30-day all-cause mortality rate, 30-day cardiovascular disease mortality rate, in-hospital all-cause mortality rate, 30-day myocardial infarction (re-infarction) rate, 30-day stroke rate, 30-day major GUSTO bleeding rate, optimal in-hospital medication use, optimal discharge medication use, tobacco cessation advice”.

8.2 Sample Size and Accrual

Power and sample size are covered in detail within the ACS QUIK Statistical Analysis Plan (Version 22 September 2014). In brief “At an alpha of 0.05, the anticipated sample size of 15,000 patients will result in 80% power to detect a 2.4% difference from a baseline 10.4% 30-day MACE rate. This sample size is increased to 15,750 to account for up to 5% drop out between discharge and 30-day follow-up.”

8.3 Data Analyses Plans

8.3.1 Data Storage

The ACS QUIK electronic database shall be used for data collection. Each hospital will be issued an account and trained on the correct usage of this monitoring system. Adverse event rates will be monitored through this system.

8.3.2 Interim Monitoring

A 5 person independent DSMB with expertise in biostatistics, ethics, clinical trials, and quality care and outcomes will perform

one interim analysis including but not limited to enrollment and serious adverse events. Reports will be electronically sent to the NHLBI and local IRBs when applicable.

DSMB Members:

- Brahmajee K. Nallamothu, MD, University of Michigan
- Thomas Alexander, MD, Coimbatore, India
- Karla Hemming, PhD, University of Birmingham
- K. R. Sundaram, M.Sc, Ph.D, Amrita Institute of Medical Sciences
- Simon Thom, MD, Imperial College London

8.3.3 Data Analysis

Interim and final analysis are covered in detail within the ACS QUIK Statistical Analysis Plan (Version 22 September 2014).

9.0 STUDY MANAGEMENT

9.1 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the applicable local ethics board. All investigators will follow the University conflict of interest policy.

9.2 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

9.3 Required Documentation

Before the study can be initiated at any site, the following documentation must be provided to the applicable ethics board.

- A copy of the protocol and informed consent
- PI Undertaking for the principal investigator and any associate investigators who will be involved in the study

The study may not be initiated before receipt of an Ethics Committee or IRB approval letter.

9.4 Registration Procedures

Patient enrollment within the study will be tracked through the ACS QUIK electronic database. Formal registration with the coordinating center is not required for this study.

9.5 Data Management and Monitoring/Auditing

Data management and monitoring are discussed in detail within the ACS QUIK Data Safety Monitoring Plan (Version 22 September 2014). In brief, the following data management and monitoring procedures are outlined in the ACS QUIK Data Safety Monitoring Plan.

"Data will be collected at the site through the ACS QUIK electronic database. Collected data will comprise the American College of Cardiology ACS Key Data Elements and Definitions for Measuring the Clinical Management and Outcomes. Data include but are not limited to socio demographics, presenting signs/symptoms, medical history (medications/habits/etc.), ECG/biomarkers, diagnostic details (echocardiography, angiography, e.g.), therapeutics details (medications, PCI, cardiopulmonary resuscitation, e.g.), major in-hospital events, discharge status/diagnosis, personal insurance status, and direct/indirect costs related to hospitalization.

Monitoring for the study is provided by the research coordinating center, the Centre for Chronic Disease Control (CCDC). Monitoring throughout the trial is through audits at selected sites and regular review by the CCDC.

The CCDC reviews study conduct including enrollment, informed consent, drop-out, protocol deviations, and AEs in aggregate on a quarterly basis Additionally, it will also be responsible for reviewing serious adverse events (SAEs) in real-time.

Sites will be subject to audits of 5% of source documents. A supplementary random sample of 5% of discharged patients will be contacted by the coordinating center to confirm existence in order to identify and minimize fraudulent data entry.

Study data will be provided to the CCDC on a biweekly basis through the electronic data capture system. These data are aggregated for each quarterly review. Data reports are prepared by the CCDC project coordinator and biostatistician.

Additionally, central statistical monitoring will performed on periodic basis by the study coordinating center to evaluate the quality of data across sites, which helps minimize site visits."

9.6 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol

9.6.1 Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval.

For any such emergency modification implemented, a IRB modification form must be completed within ten (10) business days of making the change.

9.6.2 Other Protocol Deviations/Violations

All other planned deviations from the protocol must have prior approval by the Principal Investigator and the IRB. According to the IRB, a protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs
- Has no substantive effect on the risks to research participants
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
- Did not result from willful or knowing misconduct on the part of the investigator(s).

An unplanned protocol variance is considered a violation if the variance:

- Has harmed or increased the risk of harm to one or more research participants.

- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

If a deviation or violation occurs without prior approval from the Principal Investigator, please follow the guidelines below:

Protocol Deviations: Personnel will report to any sponsor or data and safety monitoring committee in accordance with their policies. Deviations should be summarized and reported to the IRB at the time of continuing review.

Protocol Violations: The site coordinator should report violations to their site's governing IRB, and the CCDC IRB within 24 hours of the investigator becoming aware of the event.

9.7 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required

The written amendment, and if required the amended consent form, must be sent to the IRB for approval prior to implementation.

9.8 Record Retention

Study documentation includes all source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that the study investigator must retain all study documentation pertaining to the conduct of a clinical trial. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other

cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

9.9 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Site Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms.

10.0 REFERENCES

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11.0 Appendix A: Informed Consent Form

Consent Form

PROTOCOL TITLE: Acute Coronary Syndrome Quality Improvement in Kerala

PRINCIPAL INVESTIGATOR: Mark Huffman, MD MPH

CO-INVESTIGATOR: PP Mohanan MD, DM

CO-INVESTIGATOR: D. Prabhakaran, MD, DM (Cardiology), MSc, FRCP, FNASc

SUPPORTED BY: Northwestern University Feinberg School of Medicine Department of Preventive Medicine, Cardiological Society of India Kerala Chapter

SPONSORED BY: National Heart, Lung, and Blood Institute. Award 1K99HL107749-01A1

SITE INVESTIGATOR: <<Name>>

Introduction
You are being asked to take part in a research study. This document has important information about the reason for the study, what you will do if you choose to be in this research study, and the way we would like to use information about you and your health.

Conflict of Interest Disclosure
The following disclosure is made to give you an opportunity to decide if this relationship will affect your willingness to participate in this research study:

Your doctor may also be the person responsible for this research study at your hospital, please note that he/she is interested in both your clinical care and the conduct of this research study. You have the right to discuss this study with another person who is not part of the research team before making your decision whether or not to be in the study.

What is the reason for doing this study?
You are being asked to participate because you have been diagnosed with Acute Coronary Syndrome requiring care at this hospital. As a participant in this study, the hospital will contact you 30-days after you have been treated.

This hospital is part of a study determining how a quality improvement toolkit affects the rate of major adverse cardiovascular events 30-days after patients are treated. Hospitals within this study are randomized to implement a quality improvement toolkit.

Randomization means the hospital has been randomly assigned to a treatment based on chance, like a flip of a coin. Neither you nor the hospital chooses the assigned group.

How many people will take part in this study?
The study investigators hope to enroll 15,750 subjects in Kerala, India.

What will you do if you choose to be in this study?
If you consent to participate, the hospital will contact you 30 days after you have been treated to ask you questions about your health. You may also be asked to complete two other surveys about your health related quality of life and economic effects of hospitalization. The contact will either be by phone or in-person and will take approximately 30 minutes.

People who participate in this study and people who do not will not be treated any differently during their hospital stay.

What are some of the possible risks and discomforts?
We do not think you will experience any physical risk or discomfort from being contacted 30-days after treatment. One of the rare risks may be loss of confidentiality, we have taken measures to minimize this risk.

What are the Possible Benefits for Me or Others?
Taking part in this study may help scientists to better understand if use of standard documents and procedures improves the rates of adverse events after hospitalization for acute coronary syndrome.

What other procedures or courses of treatment might be available to me?
You do not have to take part in this research study. If you do not participate in this study you will receive the same treatment in the hospital.

Are there any financial costs to being in this study*?*
There will be no costs to you for being in this study.

Will I receive payment for participation in this study?
You will not be paid for your participation in this study.

If I have questions or concerns about this research study, whom can I call?
You can call us with your questions or concerns. If you have any illness or injury during your time on this study, you should call us promptly.

Your doctor is <Name>. You can call <Him/Her> at <Phone Number> during <Monday through Friday> from <8 AM to 5 PM> India Standard Time.

All contact information for your hospital may be found in Appendix A. You may also call the principal or co-investigators. Their contact information may be found in Appendix B.

What are my rights as a research subject?

If you choose to be in this study, you have the right to be treated with respect, including respect for your decision whether or not you wish to continue or stop being in the study. You are free to choose to stop being in the study at any time.

Choosing not to be in this study or to stop being in this study will not result in any penalty to you or loss of benefit to which you are entitled. Specifically, your choice not to be in this study will not negatively affect your right to any present or future medical treatment.

Any new findings developed during the course of this research that may affect your willingness to continue in this study will be shared with you.

Your participation in this study may be stopped by the investigator without your consent if the study is cancelled.

If you want to speak with someone who is not directly involved in this research or have questions about your rights as a research subject, please contact your local ethics board.

Your local ethics board is <Name>. You can call them at <Phone Number> during <Monday through Friday> from <8 AM to 5 PM> India Standard Time.

What about my confidentiality and privacy rights?

We are committed to respect your privacy and to keep your personal information confidential. When choosing to take part in this study, you are giving us the permission to use your personal health information that includes health information in your medical records and information that can identify you. For example, personal health information may include your name, address, phone number or identification number. Your health information we may collect and use for this research includes:

- All information in a medical record
- Results of physical examinations
- Medical history
- Lab tests, or certain health information indicating or relating to a particular condition as well diaries and questionnaires
- Records about medication or drugs

The following groups of people may give the researchers information about you:

- All current care providers, including but not limited to your attending physician or other hospital staff.

Once we have the health information listed above, we may share some of this information with the following people. Please note that any research information shared with people outside of the <Name of the site/hospital (which recruits the participant)> and its clinical partners (or affiliates) will not contain your name, address, telephone, identification number or any other direct personal identifier unless disclosure of the

direct identifier is required by law [except that such information may be viewed by the Study sponsor and its partners or contractors at the Principal Investigators office]

- Authorized members of the Northwestern University workforce, who may need to see your information, such as administrative staff members from the Office for Research, Office for Research Integrity and members of the Institutional Review Board (a committee which is responsible for the ethical oversight of the study),

- Study monitors and auditors who make sure that the study is being done properly,

- Government agencies and public health authorities, such as the Center for Chronic Disease Control (CCDC), Indian Council of Medical Research (ICMR), and the study sponsor the National Heart, Lung, and Blood Institute (NHLBI).

The results of this study may also be used for teaching, publications, or presentation at scientific meetings.

Please note that:

- If you do not sign this form, there will be no affect to your in-hospital treatment by health care providers, or the payment or enrollment in any health plans, or affect your eligibility for benefits. However, you will not be part of the research study. If you do sign this form, there will be no affect to your in-hospital treatment by health care providers, or the payment or enrollment in any health plans, or affect your eligibility for benefits. You will be contacted by the hospital after you are treated.
- You may change your mind and “take back” (revoke) this consent at any time. Even if you revoke this consent, the Principal Investigator may still use or share health information that was obtained about you before you revoked your consent as needed for the purpose of this study. To revoke your consent for the use of your health information, you must do so in writing to your local primary investigator (contact details are in Appendix A).
- Unless you revoke your consent, it will not expire.

Consent Summary

(Please give one copy to the participant and keep a copy for the Investigator)

Study Title: Acute Coronary Syndrome Quality Improvement in Kerala

Please read the following and place an "X" before putting your signature below:

I have read this consent form and the research study has been explained to me.	[ ]
I have been given time to ask questions, and have been told whom to contact if I have more questions.	[ ]
I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	[ ]
I understand that the Sponsor of the study, others working on the Sponsor's behalf, the Ethics Committee, and the regulatory authorities will not need my permission to look at my health records, both for the current study and any further research that may be conducted in relation to it, even if I stop taking part in the study. I understand that my identity will not be revealed in any information released to third parties or published.	[ ]
I agree not to restrict the use of any of my information or results that arise from this study provided such a use is only for scientific purpose(s).	[ ]
I have been given a copy of the information sheet and consent form to keep. By signing this form I have not given up my legal rights.	[ ]
I want to participate in the Seattle Angina Questionnaire or the Economic Survey	[ ]

I agree to be in the research study described above. A copy of the consent form will be provided to me after I sign it.

_____	_____	_____
Subject's Name (printed)	Signature	Date
_____	_____	_____
Investigator's Name (printed)	Signature	Date

For subjects unable to give consent, permission to participate is given by the following authorized subject representative:

_____ _____ _____

Legally Acceptable Representative's Signature Date
Name (printed)

My authority to sign as the subject's authorized representative.

☐ Parent ☐ Spouse
☐ Legal Guardian ☐ Authorized Agent (e.g., Health Care Power of Attorney)

Appendix A: Local Contact Details

Hospital Name:

Site Investigator Name:

I can be contacted by phone at:

I can be contacted in writing at:

On: ☐ Monday ☐ Tuesday ☐ Wednesday ☐ Thursday ☐ Friday ☐ Saturday ☐ Sunday

From: ☐ Any Time ☐ Hours:

Nurse/Study Coordinator Name:

I can be contacted by phone at:

On: ☐ Monday ☐ Tuesday ☐ Wednesday ☐ Thursday ☐ Friday ☐ Saturday ☐ Sunday

From: ☐ Any Time ☐ Hours:

Ethics Board Name:

I can be contacted by phone at:

On: ☐ Monday ☐ Tuesday ☐ Wednesday ☐ Thursday ☐ Friday ☐ Saturday ☐ Sunday

From: ☐ Any Time ☐ Hours:

Emergency Telephone:

This number can be called at any time.

Appendix B: Alternate Contact Details

Principal Investigator Name:	Dr. Mark Huffman	
I can be contacted by phone at:	+1 312 503 0734	Monday through Friday from 8 AM to 5 PM Central Standard Time
I can be contacted in writing at:	MHuffman@nmff.org	Anytime
Co-Investigator Name:	Dr. PP Mohanan	
I can be contacted by phone at:	+91 0484 2706422	Monday through Friday from 8 AM to 5 PM India Standard Time
I can be contacted in writing at:	drppmohanan@gmail.com	Anytime