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

Statistical Analysis Plan
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Prepared for:
Northwestern University/Central Coordinating Centre

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1. Introduction

This statistical analysis plan (SAP) describes the planned analysis and reporting for Northwestern University Protocol (Version 22 September 2014) “Acute Coronary Syndrome Quality Improvement in Kerala (ACS QUIK)”, a cluster-randomized, stepped wedge clinical trial that aims to implement and evaluate the effect of a locally-developed quality improvement toolkit on 30-day major adverse cardiovascular event rates in patients admitted with acute coronary syndrome in Kerala.

The structure and content of this SAP provide sufficient detail to meet the requirements identified by the Food and Drug Administration and International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): Guidance on Statistical Principles in Clinical Trials. All work planned and reported for this SAP will follow internationally accepted guidelines, including those published by the American Statistical Association and the Royal Statistical Society, for statistical practice.

The following documents were reviewed in preparation of this SAP:

- In-Hospital (Version 18 September 2014) and 30-day Follow Up (Version 18 September 2014) Case Report Forms (CRFs).
- ICH Guidance on Statistical Principles for Clinical Trials.

The reader of this SAP is encouraged to also read the study protocol for details on the conduct of this study and the Data Management Plan for details regarding data review, cleaning, and management. The analysis plan also outlines the proposed layout of tables and figures that will be presented.

2. Study objectives

2.1. Efficacy

2.1.1. Primary objective

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.

2.1.2. Secondary objective

- To evaluate 30-day health related quality of life in patients with acute coronary syndrome using a translated and validated version of the Seattle Angina Questionnaire (SAQ).
- 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.
- 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.

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

### 2.2. Safety

The intervention does not include implementation of any new drug nor invasive procedure. Rather, the intervention will occur at the health system level in an effort to increase the use of evidence-based therapies for the management of patients admitted with acute coronary syndromes. Because patients hospitalized with acute coronary syndromes are expected to have adverse events and serious adverse events, we will capture in-hospital and 30-day major adverse cardiovascular events. We will collect information regarding unexpected adverse events, which may be related to implementation of the intervention.

### 3. Study design

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 2. Stepped Wedge Design**

*Denotes randomization at beginning of the study to cohort group, n = 12 hospitals per cohort.

** Denotes progression from usual care to intervention by locally-developed quality improvement toolkits.
4. **Sample size**

Power and sample size are calculated based on a cluster randomized stepped wedge design (STATA v.12). The average anticipated cluster size is based on previous data from the Kerala ACS Registry. Intraclass correlation (ICC) is set to 0.05 based on the comparable BRIDGE ACS study (Berwanger et al. *JAMA* 2012; 307:2041) and ICC from the Kerala ACS Registry in-hospital MACE rate.

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.

5. **Randomization**

The biostatistician at the central coordinating center (Centre for Chronic Disease Control) will centrally randomize the clusters using a computer generated randomization sequence and maintain privacy of randomization records prior to the beginning of the data collection on a password protected secure server. Stratified (based on hospital size) randomization will be used to randomize one cohort of hospitals to receive the intervention in each of the four time periods. These strategies will be used to minimize selection bias through sequence generation and allocation concealment. The group of hospitals that are randomized to the intervention in the final step will know that they will be randomized ahead of time, but we know of no other strategy to minimize this bias. No other group of hospitals will be aware of where they fall on the allocation schedule. Local investigators will be notified three weeks in advance of the start date for the quality improvement project at their hospital.

6. **Study endpoints**

6.1. **Efficacy**

6.1.1. **Primary endpoint**

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)). Because these data will be collected at the site-level, the outcome assessors will not be blinded. However, there does not appear to be evidence of outcome assessment bias in the case of objective outcomes (OR [95% CI] 1.01 [0.92, 1.10], Wood L, et al. *BMJ*, 2008; 336:601).

6.1.2. **Secondary endpoints**

- 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
6.1.3. Implementation of intervention
We will also evaluate the degree to which the intervention is implemented to evaluate for potential type III error through the number and frequency of downloads of quality improvement materials (standard order sets, audit and feedback reports) and number and frequency of quality improvement team meetings by self-report. These quantitative data can be used in sub-group analyses to evaluate if the effect of the intervention is modified by the use of the quality improvement materials. We will complement this quantitative evaluation with a mid-trial qualitative evaluation of sites through interviews and focus group discussions, as recommended by the UK Medical Research Council guidelines on complex interventions (Craig P, et al. MRC, 2008).

6.1.4. ACS QUIK sub-studies
We also aim to evaluate the effect of the intervention on two sub-studies on sub-sample of 2200 subjects:

- Health related quality of life at 30 days, using a translated and linguistically validated version of the Seattle Angina Questionnaire (SAQ).
- Individual and household level impoverishing effects of an ACS event and compare against historical data (Huffman MD, et al. PLoS ONE, 2011: e20281) to evaluate the effect of a national government insurance program for families below the poverty line.

We will also evaluate the association between concordance of in-hospital and discharge medical therapy (>80% of recommended drugs [in-hospital and discharge]) and 30-day MACE rates.

6.2. Safety
At the recommendation of the Data & Safety Monitoring Board, we will collect and report data on serious adverse events and unanticipated adverse events. All patients will be under the care of a hospital-based medical team for their usual care, including the diagnosis and treatment of any serious or unexpected adverse events.
7. Statistical Analysis

7.1. General Principles
Data analyses will be performed at Central Coordinating Centre (CCC) at the Centre for Chronic Disease Control in New Delhi, India. Only de-identified data will be analyzed by the team at Northwestern University. This SAP will be finalized prior to the database lock. The statistical analysis will be performed using STATA Version 12.0, SAS, and R-program. The analysis will be performed on the principle of ‘intention to treat’ unless otherwise specified (i.e., all patients recorded in the database during the 24 month period will be included, and considered exposed to the intervention according to randomization regardless of when the intervention was actually implemented). The intervention start for each cluster will be fixed regardless of whether implementation proceeds on time. The stepped wedge design is in effect a matched design with before and after comparisons for each cluster randomised. Random effect models will be used to account for the within cluster correlation (Hussey and Hughes, 2007). Methods for handling missing data for the primary and secondary endpoints are described below.

Individual-level data will be summarized using descriptive statistics (i.e., number of subjects [n], mean, standard deviation [SD], median, minimum, and maximum) for continuous variables, and using frequency and percentage (i.e., number and proportion of subjects [n, %]) for discrete/categorical variables, unless specified otherwise. We will also report data on number and sizes of clusters. Participant-level data from the electronic data capture (EDC) system and any derived variables will be reported.

7.2. Missing data handling
If the data are “not obtained” on the 30-day follow-up assessment form following the outpatient department follow-up visit or after three telephone call attempts by the site coordinator, then data will be considered as missing. We will perform sensitivity analyses using complete case analysis and multiple imputation to evaluate the potential effect of missing outcomes.

7.3. CONSORT statements for reporting trials of non-pharmacologic interventions and cluster-randomized trials
All participants who were screened and invited to participate in this trial will be accounted for, in accordance with the CONSORT statements for reporting trials of non-pharmacologic interventions (Boutron I, et al. Ann Int Med 2008; 148:295) and cluster-randomized trials (Campbell MK, et al. BMJ 2012; 345:e5661). Reasons for early withdrawal will be listed for all participants that prematurely discontinued the study. The number of participants that were registered but not randomized will be presented and the reasons for non-participation.
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7.4. Patient disposition
Number of patients who were registered, fulfilled eligibility criterion, together with the reasons for exclusion, and the number randomized by study center will be summarized. Baseline demographic variables such as age, gender, and relevant clinical variables (e.g. smoking status, medical history, blood pressure and cholesterol) will be summarized for each group. Summaries of continuous baseline variables will be presented as means and standard deviations together with medians and minimum and maximum values. Categorical variables will be described as frequencies and percentage (appendix for a list of tables that will be used for presenting baseline characteristics).

7.5. Primary endpoint analyses
The primary outcome will be 30-day major adverse cardiovascular event (MACE) rate. Overall differences in 30-day MACE rates between control and intervention periods will be reported. In the primary analysis, 30-day MACE will be modelled using mixed effects logistic regression with random cluster (hospital) effects and including a fixed time effect within every 4 months periods. Baseline data collected from the first time period will be tabulated by order of implementation, 12 clusters in 5 groups. The adequacy of randomization will be examined and any hospital level variable unbalanced at baseline will be included in the model as sensitivity analysis. The patient level covariates included will be finalized prior to unblinded statistical analysis.

7.5.1. Adjusted Analyses
In case of some general individual information will be not balanced between two groups, a sensitivity analysis will be performed, by adjusting for those factors in the format of a GRACE adjusted risk score.

7.5.2. Subgroup Analyses
The following a priori sub-group analyses will be carried out to evaluate potential heterogeneity of effect.

- Site level characteristics
  - Hospital size
  - Use of quality improvement toolkit components

- Participant level characteristics
  - Age (<65 years and >65 years)
  - Sex
  - ST segment elevation myocardial infarction vs. non-ST segment elevation myocardial infarction

7.6. Secondary endpoint analyses
Secondary outcomes 30-day all-cause and cardiovascular death, in-hospital death, 30-day myocardial infarction (re-infarction), 30-day stroke, 30-day major GUSTO bleeding will be analyzed using mixed effects logistic regression. We will also evaluate the proportion of patients receiving optimal in-hospital medication use, optimal
discharge medication use, and tobacco cessation advice between intervention and control groups.

7.7. Sub-studies
We will evaluate the effect of the intervention of health-related quality of life and individual and household level impoverishing effects. We will also evaluate the association between concordance of in-hospital and discharge medical therapy and 30-day MACE rates.

7.8. Safety analysis
All serious and unanticipated adverse events data will be reported. Serious adverse events (SAEs) are defined as any adverse event that 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. SAEs will be routinely captured through the electronic data capture form and reported semi-annually and at the interim safety analysis. By definition, unanticipated adverse events are not previously anticipated by the investigators but are defined as:

- Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

- Related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized (HHS, 45 CFR, part 46).

7.9. Interim analysis
Interim analysis for efficacy will be performed after one year. The analysis will assess MACE rates at hospitals operating per usual care and compare with MACE rates at hospitals in steps 1 and 2 after implementation of the quality improvement threshold. To adjust for one interim analysis, the O’Brien Fleming stopping boundary for the interim analysis will be set at $z=2.797$, $p\text{-value} < 0.005$ and for the final analysis to $z=1.977$, $p\text{-value} < 0.048$. In addition, consideration would be given to the consistency between effects seen on the primary endpoint and those seen in the secondary endpoints. Interim analysis for adverse events will be performed on a semi-annual basis. The DSMB will review the reports and make recommendation about continue or stop the study based on the interim analysis results.
7.10. Independent Data and Safety Monitoring Board (DSMB)

The study will use an independent DSMB to evaluate the outcome and safety data in the context of the overall study. The DSMB will review the data at least once per year. The study biostatisticians will discuss, independently of the Steering and management committees, the needs of the DSMB in terms of what data presentations and/or analyses of the data they wish to see and how often. A subset of the shell tables (Version 17 September 2014) prepared for the ACS QUIK study can be used for the DSMB reports.