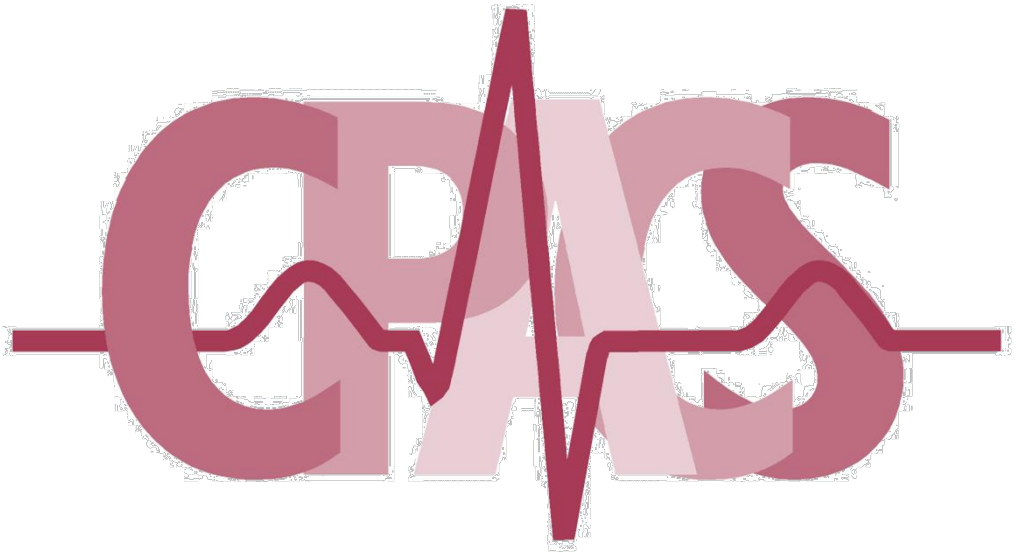


Clinical Pathways for Acute Coronary Syndromes in China

– Phase 3

Quality Improvement Initiative to Reduce Cardiovascular Events among Patients with Acute Coronary Syndromes in Resource-Constrained Hospitals in China: A Stepped-Wedge Cluster Randomized Trial

Statistical Analysis Plan

Version 2.2 June 24, 2016

by Xian Li & Shenshen Li

STATISTICAL ANALYSIS PLAN APPROVAL SHEET

Study: CPACS-3

Version: 2.2 (final)

Version date: 24 June 2016

The undersigned have reviewed this plan and find it to be consistent with the requirements of the protocol as it applies to their respective areas. The principal author also finds this plan to be in compliance with ICH-E9 as well as The George Institute's SOP ST-SOP-04.

Signature:_____ **Date**_____

Xian Li, CPACS-3 Statistician

Signature:_____ **Date**_____

Shenshen Li, CPACS-3 Research Fellow

Signature:_____ **Date**_____

Yangfeng Wu, CPACS-3 Principal investigator

Signature:_____ **Date**_____

Anushka Patel, TGI Chief Scientist

1 Study aims:

The primary aim of CPACS-3 study is to test whether the routine use of a multi-faceted quality of care improvement initiative will lead to a measurable reduction in the number of in-hospital major adverse cardiovascular events (MACE, including total death, non-fatal myocardial infarction and stroke) in patients with ACS presenting to resource-constrained hospitals in China, which was defined as the level two hospitals without PCI facilities and it requires more than 90 min. to transfer patients to the nearest medical centers from these hospitals.

The secondary aims include:

a) To determine whether the routine use of the initiative will improve quality of care.
b) To determine the major system-level facilitators and barriers to implementation and uptake of the initiative in resource-constrained settings in China.
c) To determine the cost-effectiveness of the initiative compared to usual care, from the perspective of the health care provider.

This Statistical Analysis Plan (SAP) will not cover the secondary aims b) and c), since aim b) requires a qualitative study and the way aim c) will be addressed depends upon the results of the primary study, and thus its SAP will be developed separately later. This SAP will be finalized and approved before any analyses with unblinded data.

2 Study Design

CPACS-3 study is a stepped-wedge cluster-randomized trial conducted in 104 resource-constrained hospitals from 15 provinces in China. Patients with acute coronary syndromes (ACS) will be recruited consecutively, with an anticipated total of 25,000 patients recruited within 30 months. All eligible hospitals will be randomised (stratified by province) to 4 wedges. Each wedge contains 26 hospitals. During the first 6 months data will be collected from all hospital participants without any intervention being implemented. Afterwards, the intervention will be implemented sequentially, starting with the first group of 26 hospitals (wedge 1). The second group of hospitals (wedge 2) will start the intervention 12 months later and wedges 3 and 4 will start the intervention at 18 and 24 months later respectively: see Figure 1. By 30 months, all hospitals would have had the intervention implemented for at least 6 months and final data will be collected at this time.

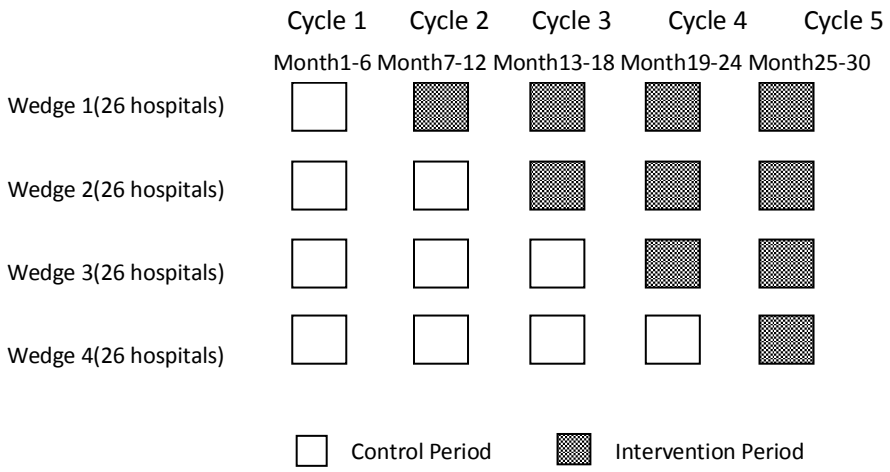
The intervention will be applied at the level of the hospital, with outcomes measured at the patient level. The ACS quality of care improvement initiative includes six components:

1. Leadership strengthening and establishment of QCI leaders group
2. Implementation of clinical pathway

3. Hospital performance audit and feedback
4. Training of physicians and nurses
5. Online technical support, and
6. Patient education

All patients discharged alive from hospital will be followed up 6 months later by telephone call.

Figure 1. Visual representation of the stepped wedge design used in CPACS 3



3 Evaluation Outcomes

Primary outcome

The primary outcome is in-hospital major adverse cardiovascular events (MACE), a composite outcome including all-cause mortality, myocardial infarction or re-infarction and stroke. The in-hospital all-cause mortality include patients who died in hospital, those who gave up treatment but died within 1 week after returning home, and those who transferred to upper level hospitals but died within 24 hours.

Secondary outcome

The following secondary endpoints will be considered:

1) In-hospital all-cause deaths.
2) A patient-level composite score is formed by dividing the total number of pre-defined binary key performance indicators (KPIs) a patient receives (numerator) by the total sum of KPIs a patient is eligible to receive (denominator). However, the length of stay will not be used for the calculation of the composite score.
3) Each of the 16 KPIs (15 binary and 1 continuous) of ACS care defined in below table.

4) A composite of MACE and re-hospitalization due to cardiovascular disease within 6 months after discharge.

Definitions of 16 KPIs of ACS care		
KPIs	Definition	Denominator
First ECG in time	The patient received the first ECG recorded within 10 minutes after hospital arrival	All patients
Early use of aspirin	The patient received aspirin within 24 hours of arrival at hospital	All patients
Early use of Clopidogrel	The patient received clopidogrel within 24 hours of arrival at hospital	All patients
Early use of statin	The patient received statin within 24 hours of arrival at hospital	All patients
Aspirin prescribed at discharge	The patient prescribed aspirin at hospital discharge	Patients discharged alive
Clopidogrel prescribed at discharge	The patient prescribed clopidogrel at hospital discharge	Patients discharged alive
Beta-blocker prescribed at discharge	The patient prescribed a beta-blocker at hospital discharge	Patients discharged alive
Statin prescribed at discharge	The patient prescribed a statin at hospital discharge	Patients discharged alive
ACEI or ARB prescribed at discharge in the presence of LVSD	The patient with left ventricular systolic dysfunction (LVSD) was prescribed angiotensin- converting–enzyme inhibitors (ACEI) or angiotensin-receptor blockers (ARB) at discharge (LVSD is defined as chart documentation of a left ventricular ejection fraction less than 40% or a narrative description of left ventricular systolic function consistent with moderate or severe systolic dysfunction)	Patients discharged alive and with LVSD less than 40% or heart function grade (KILLIP or NYHA)>=3
STEMI receiving reperfusion (fibrinolysis) therapy	The STEMI patient with ST-segment elevation or LBBB on the ECG and arrive hospital within 12 hours of symptom onset received fibrinolysis within 12 hours of symptom onset.	STEMI patients that arrived hospitals within 12 hours
Acceptable door to needle time	The STEMI patient received fibrinolytic therapy within 30 minutes of arrival at hospital.	STEMI patients that arrived hospitals within 12 hours and received fibrinolytic

		therapy
Diagnosis consistent with ECG and biomarker findings	The patient had its final diagnosis consistent with ECG and biomarker findings	All patients
Length of stay	Number of days of hospitalization	All patients
Three newly added KPIs	**Due to the changes in clinical guidelines and clinical practice, it is appropriate to add in the following new indicators.**	
Dual antiplatelet therapy	The patient received both aspirin and clopidogrel within 24 hours of arrival at hospital	All patients
Loading dose dual antiplatelet therapy	The patient received both aspirin and clopidogrel with loading dose (i.e. 300 mg or above for each medicine) within 24 hours of arrival at hospital	All patients
Loading dose statin therapy	The patient received statin with loading dose (i.e. 40 mg or above of atorvastatin or equivalent) within 24 hours of arrival at hospital	All patients

*: STEMI: ST-elevated myocardia infraction; NSTEMI: non-ST-elevated myocardia infraction; UA: Unstable angina.

4 Power

Data from our previous CPACS studies estimated the primary outcome to be 8.6% in level two hospitals and the unadjusted and adjusted intervention effect size was 12% and 59% [reference 1]. With an improved and better coordinated intervention in CPACS-3, we believe that an expected effect size of 15% to 20% reduction of primary outcome should be reasonable. Assuming an event rate of 8% for the primary outcome and $\alpha = 0.05$, a study with 96 hospitals and 40 patients per cycle from each hospital will provide 98% and 85% power to detect relative risk reduction of 20% and 15%, respectively in the primary outcome. The sample size calculations are based on the assumptions that there is no delay in the effect of the intervention and an intra-class correlation coefficient of 0.10. To account for possible drop out of participating hospitals, a total of 104 hospitals will be recruited.

5 Data collection

Baseline characteristics for both hospital and patients were collected. For hospital characteristics, data were collected at the beginning of the study. These included: level of hospital, hospital capacity (number of beds, number of medical personnel, number of outpatient services, number of emergency services), and relevant facilities (including cardiac

catheterization room and hospital information system).

For each patient enrolled into the study, the following information will be collected:

- socio-demographic variables (income, working class status, education);
- symptoms and signs relating to the presenting ACS;
- medical history, electrocardiographic and biomarker findings;
- details of investigations performed;
- details of treatments administered prior to admission, during hospitalization and at death or hospital discharge;
- final diagnosis and discharge status;
- major in-hospital clinical events (stroke, myocardial infarction, re-infarction, major bleeding episodes);
- personal insurance status and cost relating to hospitalization.

One follow-up survey (by clinic visit or telephone) will be conducted by trained hospital staff at 6 months after discharge, to collect information on medications for ACS secondary prevention, MACE and any re-hospitalizations following discharge.

6 Statistical analysis

6.1 Analysis Principles

The analyses will be conducted by intention-to-treat. All statistical tests will be two-tailed. Treatment effect for the primary and secondary outcomes will be considered significant at α=0.05. We will not adjust for multiplicity.

We will not impute values unless specified otherwise. We will report the number of observations used in each analysis. Summaries of continuous variables that are normally distributed will be presented as means and SDs and skewed data will be presented as medians and inter-quartile intervals. Categorical variables will be presented as frequencies and percentages.

All analyses on outcomes will be at individual level but account for the clustering of patients in the same hospitals using appropriate statistical models. And except for model 1, all models will be adjusted for time (i.e. “6-month cycle”).

6.2 Eligible sample size for analyses

Our analyses will include only patients with final diagnosis of STEMI, NSTEMI, and UA with non-missing discharge status (primary outcome) who also meet the inclusion and exclusion criteria defined by the study protocol.

The eligible sample size by wedges and by cycles will be presented in **Table 1**

The eligible sample size at each hospital will be presented in **Table 2**.

6.3 Characteristics of patients at baseline and comparison

Description of the demographics and baseline characteristics will be presented in **Table 3** by randomized groups (wedges), and then perform the significance test among 4 groups using linear regression with generalized estimating equations (GEE) for continuous variables and logistic regression with GEE for category variables (GEE to adjust for clustering within hospitals) to see if there is any imbalance among randomized groups (, or speak, among groups initiating the intervention at different time). The continuous variables will be presented as means and standard deviations, or medians and inter-quartile range, as appropriate.

Description of the demographics and baseline characteristics by cycle will be presented in **Table 3.1.**

Description of the demographics and baseline characteristics by intervention and control will also be presented (**Table 4)**, and test the statistical significance of each variable.

6.4 Main efficacy analyses for the primary outcome

Simple description of primary outcome

The raw percentage of in-hospital MACE will be summarized as n (%) by wedge and cycle (**Table 5**) and by intervention and control (**Table 5.1**).

Model analysis for primary outcome

In a stepped wedge design more clusters are exposed to the intervention towards the end of the study than in its early stages (one-way). This implies that the effect of the intervention might be confounded with any underlying temporal trend. A result that initially might seem suggestive of an effect of the intervention may therefore transpire to be the result of a positive underlying temporal trend, or vice versa. [reference 2] That means we will adjust for time in primary analysis.

The primary analysis will use generalized estimating equations (GEE), an extended form of logistic regression, to compare the odds of in-hospital MACE between intervention and control using all periods' data. Cycle (every 6 months) will be taken as a fixed effect, with an exchangeable correlation structure to account for clustering (the correlation within hospitals). [reference 3] A robust standard error will be used to guard against misspecification of the correlation structure.

Model 1

Firstly, we will fit a model (**Model 1**) in which we will include the main effect of intervention only,

$$Logit(p_i) = \beta_0 + \beta_1 Intervention + e_i$$

Where e_i means the random error in ith patient.
Then, we will examine if there is a time effect in the following two ways:

Model 2 (primary analysis)
Assuming the time effect is non-linear, we will include the main effect of intervention and time (cycle) into Model 2, with cycle treated as a categorical variable (with the first cycle as the reference category) to test if there is a significant intervention effect after adjusting for the time effect.

The log odds of MACE in Model 2 for the ith patient can be written as:

$$Logit(p_i) = \beta_0 + \beta_1 Intervention + \beta_2 cycle2 + \beta_3 cycle3 + \beta_4 cycle4 + \beta_5 cycle5 + e_i$$

Model 3
Assuming the time effect is linear, we will include the main effect of intervention and time (cycle) into Model 3, with cycle treated as a continuous variable. The log odds of MACE in Model 3 for ith patient can be written as:

$$Logit(p_i) = \beta_0 + \beta_1 Intervention + \beta_2 cycle + e_i$$

The model 2 and 3 will be done whatever the main effect of intervention in Model 1 will be significant or not.

Model 4
If there is no significant time effect in Model 2 and 3, Model 4 won't be conducted.

If there is a significant time effect, either in Model 2 or 3, we will fit a full model with a time*intervention interaction term, in which the interaction between intervention and time will be tested to see if there is an additional effect over time after initiating the intervention. The probability of MACE in Model 4 for ith patient then can be written as:

$$Logit(p_i) = \beta_0 + \beta_1 intervention \quad + \beta_2 time \quad + \beta_3 intervention \quad * time \quad + e_i$$

With time as a categorical or continuous variable.

In case of an additional effect of time does not exist, the interaction term will be removed from this model, that is, return to Model 2 and 3.

Adjusting for potential confounders at patient level and hospital level:
All models will have unadjusted analysis and adjusted analysis for the patient-level covariates or hospital-level covariates to account for the potential confounding from baseline characteristics. All adjusted analyses will be considered as secondary. Three-level generalized linear-mixed models with hospital and province as second and third levels, respectively, will be used in the adjusted analysis. Exploratory analysis on covariates (eg. univariate modeling,

scatter plot) will be conducted and only those that are either significantly associated with the outcomes (P<0.05) or have strong clinical importance will be further added to the model. Potential interaction terms between them will be also examined similarly afterwards.

The resulting odds ratios of all the fixed effects from the Model 1 to Model 3 (unadjusted and adjusted), as well as their 95% CIs, will be reported along with their respective p-values in **Table 6 to Table 8**.

In the rare case that the GEE models do not converge, the Quadratic Inference Function (QIF) [reference 4] will be used as an alternative approach. Unlike GEE, the estimator function of QIF is bounded and approaches zero, so the QIF estimator improves the efficiency of GEE when the working correlation is misspecified and remains as efficient as GEE when the working correlation is correct.

6.5 Analysis for in-hospital all-cause mortality (secondary outcome)

For the analysis of in-hospital all-cause mortality, we will use a similar analysis strategy and similar models to the primary outcomes.

The raw percentage of in-hospital all-cause mortality will be summarized as n (%) by wedge and cycles (**Table 9**) and by intervention and control (**Table 9.1**).

Repeat model 1 to model 4 for in-hospital all-cause mortality, the resulting odds ratios (or coefficients) of all the fixed effects from Model 1 to Model 3 (unadjusted and adjusted), as well as their 95% CIs, will be reported along with their respective p-values in **Tables 10-12**.

6.6 Analysis for the composite score of KPIs (secondary outcome)

Based on 15 pre-defined binary KPIs, except for the length of stay, we will develop a composite score by simply sum up them with giving each KPI one score, and then normalize the score by dividing the sum by the number of eligible KPIs to the specific patient.

A simple description for the composite score by wedges and by cycles will be presented in **Table 17** (similar format to Table 5) and by intervention and control in **Table 13.1**.

Model 1 to model 4 (unadjusted and adjusted) will be applied to the composite score except that linear regression with GEE will be used instead of logistic regression with GEE for all the model analyses.

In a similar format to Table 6 to Table 8, the results of all the fixed effects from Model 1 to Model 3 (unadjusted and adjusted) for the composite score will be presented in **Table 14 to Table 16,** in which the regression coefficients will be also reported along with the odds ratios.

6.7 Analysis for 16 KPIs (secondary outcomes)

We will conduct similar descriptive analyses and apply model 1 and 2 to 16 KPIs. For 15 binary KPIs, logistic regression with GEE model will be used and odds ratios will be reported, and for the continuous KPIs, linear regression with GEE will be used instead of logistic regression with GEE and the regression coefficients will be reported instead of odds ratios.

A simple description for 16 KPIs by wedges and by cycles will be presented separately in **Table 17** to **Table 32** (similar format to Table 5). And the simple description of them by intervention and control will be presented separately in **Table 17.1 to Table 32.1** (similar format to Table 5.1).

In a similar format to Table 6 and Table 7, the results from Model 1 and Model 2 (unadjusted and adjusted analysis) for each KPI will be presented as **Table 33 to Table 64**.

6.8 Analysis for a composite endpoint of MACE and re-hospitalization due to cardiovascular disease within 6-month after discharge (secondary outcome)

When performing the analysis for this endpoint, the follow-up rate (**Table 65**) will be examined. Should this exceed 10%, comparison between those followed up and those lost to follow up will be investigated. We will use Student's t test or chi-square to compare the baseline characteristics of ACS patients who completed the 6-month follow-up (completers) and those who did not (non-completers) because of withdrawal or loss-to-follow-up (**Table 66**).

A simple description for 6-month follow-up endpoint by wedges and by cycles will be presented in **Table 67 (**similar format to Table 5) and that by intervention and control in **Table 67.1**.

Model 1 to Model 4 (unadjusted and adjusted) will be applied. Similar to Table 6 to Table 8, the resulting odds ratios of all the fixed effects from the Model 1 to Model 3 (unadjusted and adjusted) for 6-month follow-up endpoint, as well as their 95% CIs, will be reported along with their respective p-values in **Table 68 to Table 70.**

6.9 Intra-cluster coefficient for outcomes

The Intra-cluster coefficient (ICC) for primary outcome and all the secondary outcomes will be estimated from all periods' data. (**Table 71**)

6.10 Sensitivity analyses

During the study operation and data management, the study team developed two indices: a quality index and an intervention index. The quality index is based on the clinical research associates (CRAs) evaluation of the study performance of each hospital (the percentage of data items that could not be verified for CRA reviewed cases).

We will repeat the above descriptive analyses and Model 2 for the primary outcome and the two secondary outcomes (in-hospital total death and the composite score of KPIs), after excluding those hospitals with poor data quality and compare the results with the main analyses to help us to draw final conclusions.

The simple description for primary outcome by wedges and by cycles after excluded hospitals with poor quality of data will be presented in **Table 72 (**similar to Table 5) and by intervention and control in **Table 72.1**.
The results of model 2 (unadjusted and adjusted) for primary outcome after excluding hospitals with poor quality of data will be presented in **Table 73**, similar to **Table 7.**

The simple description for in-hospital all-cause mortality by wedges and by cycles after excluded hospitals with poor quality of data will be presented in **Table 74 (**similar to Table 9) and by intervention and control in **Table 74.1**.
The results of model 2 (unadjusted and adjusted) for in-hospital all-cause mortality after excluding hospitals with poor quality of data will be presented in **Table 75**, similar to Table 11.

The simple description for the composite score of KPIs by wedges and by cycles after excluded hospitals with poor quality of data will be presented in **Table 76 (**similar to Table 13) and by intervention and control in **Table 76.1**.
The results of model 2 (unadjusted and adjusted) for the composite scores after excluding hospitals with poor quality of data will be presented as **Table 77**, similar to Table 15**.**

During the site monitoring, our CRAs recorded 6 evaluation fields, from each hospital, about how well each intervention was implemented. An intervention index was made based on these field notes to objectively evaluate the implementation and completion of intervention.

The results of Model 2 analysis (unadjusted and adjusted) for in-hospital MACE when further adjusted the intervention index will be presented in **Table 78**, similar to table 7**.**

The results of Model 2 analysis (unadjusted and adjusted) for in-hospital all-cause mortality when further adjusted the intervention index will be presented in **Table 79**, similar to table 11**.**

The results of Model 2 analysis (unadjusted and adjusted) for the composite scores when further adjusted for the intervention index will be presented as **Table 80**, similar to table 15**.**

7 References

1. Du X, Gao R, Turnbull F, et al. Hospital Quality Improvement Initiative for Patients With Acute Coronary Syndromes in China: A Cluster Randomized, Controlled Trial. Circulation. Circ Cardiovasc Qual Outcomes. 2014;7:217-26
2. Hemming K, Haines TP, Chilton PJ, Girling AJ, Lilford RJ. The stepped wedge cluster randomised trial: rationale, design, analysis, and reporting. BMJ. 2015 Feb 6; 350: h391.
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4. Qu AP, and Song PXK (2004). Assessing robustness of generalized estimating equations and quadratic inference functions. Biometrika 91, 447-459.