Drug Substance	
Study Number	ISSBRIL0166
Version Number	Version 6.0
Date	16th July 2014

A Cluster Randomised Trial of Objective Risk Assessment versus standard care for Acute Coronary Syndromes

Investigator Signature Page

1.1 Title of the Study: Australian Grace Risk Implementation study (AGRIS)

The Steering Committee approves the contents of this protocol and agrees the protocol contains the information required for the proper conduct of this study.

Steering Committee Chairs;

Name: Professor David Brieger	Sign:	Date:
Name Professor Derek Chew		

To indicate your agreement with the protocol, please sign and date below:

AGREED AND ACCEPTED
PRINCIPAL INVESTIGATOR
[Insert Name]
[Insert Date]

TABLE OF CONTENTS PAGE

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
ACACIA	Australian acute CoronAry Syndrome ProspeCtIve Audit
ACS	Acute Coronary Syndrome
ACUITY	Acute Catheterization and Urgent Intervention Triage Strategy
Angio	Coronary Angiogram
BBB	Bundle Branch Block
CABG	Coronary Artery Bypass Graft
CPK	Creatine phosphokinase
CPK-MB	Creatine phosphokinase-MB
CT	Computerized Tomography scan
DCF	Data Collection Form
DOB	Date of Birth
DM	Data Management
ECG	Electrocardiogram
EF	Ejection Fraction
GCP	Good Clinical Practice
GEP	Good Epidemiological Practices
GRACE	Global Registry of Acute Coronary Events
HB	Haemoglobin
ICH	International Conference of Harmonization
IRB/IEC	Institutional Review Board / Independent Ethics Committee
LBBB	Left Bundle Branch Block
MI	Myocardial Infarction
MRI	Magnetic Resonance
MR	Mitral Regurgitation
NSTEMI	Non-ST Elevation Myocardial Infarction
PCI	Percutaneous Coronary Intervention
SAP	Statistical Analysis Plan
STEMI	ST Elevation Myocardial Infarction
TIA	Transient Ischemic Attack
TIMI	Thrombolysis in Myocardial Infarction
VT	Ventricular Tachycardia

1. INTRODUCTION

Clinical risk stratification is the essential step in the effective and efficient translation of proven therapies into improved clinical practice. Yet, in acute coronary syndromes (ACS) care, we know that clinical risk assessment based on physician perception is heterogeneous. This study seeks to enhance evidence-based decision-making and outcomes by evaluating the impact of objective risk score-based decision-making using the GRACE risk tool together with recommendations for evidenced based care versus standard care in a hospital-level cluster-randomised implementation trial.

2. BACKGROUND

2.1 Potential opportunities for reducing morbidity and mortality in Australian ACS care.

Outcomes among the many patients presenting with ACS are compromised by the imperfect use of currently available therapies. Examples from the Australian clinical context observe that reperfusion for ST elevation myocardial infarction (STEMI) is provided in only 70% of eligible patients and complete prescription of guideline-advocated discharge therapies are provided in only 43% of patients.[1,2] Further contemporary evidence of this comes from the SNAPSHOT ACS study.

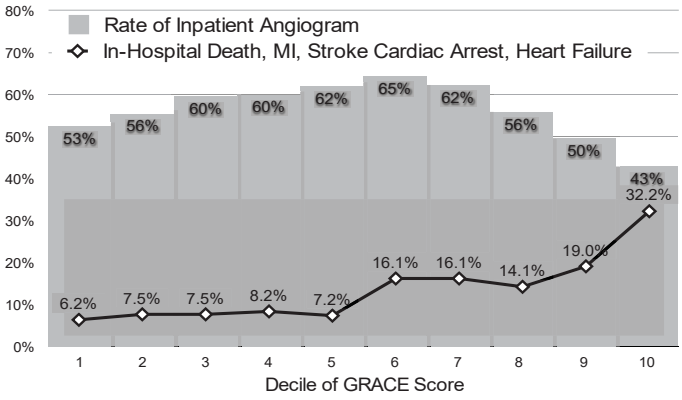

Figure1. High risk patients receive less invasive management.

Among the 2365 ACS patients enrolled from 286 participating hospitals within a 2-week period, a steep decline in the provision of early invasive management with increasing GRACE score in the upper deciles is still seen despite an increase in in-hospital death, recurrent myocardial infarction, stroke, cardiac arrest and new onset heart failure (Figure 1). Ample local and international evidence demonstrates poorer long-term outcomes among patients not receiving evidence-based therapies. Closing this evidence gap represents a near-term goal in health agendas around the world. *The key translational challenge resides in defining those interventions that may bridge this evidence practice gap in an effective and cost-effective manner.*

2.2 Clinical Risk Stratification: A translation gap

2.2.1 Limited objectivity in the provision of care: Previous studies have illustrated a disconnect between physician-perceived use of guideline-based therapies and their actual use by surveying physicians at each hospital upon completion of a site-specific audit in the ACACIA study.(1) Overall, correlation between perceived and actual use for guideline therapies was very poor (highest correlation $r=0.31$ ($p<0.01$) for use of invasive management)

with perceived grossly overestimating actual use (Figure 2). In contrast, when clinical guideline content was assessed, clinicians scored highly (~70%), underlining that *difficulties in translating knowledge, rather than the lack of knowledge per se, may explain this disconnect*.

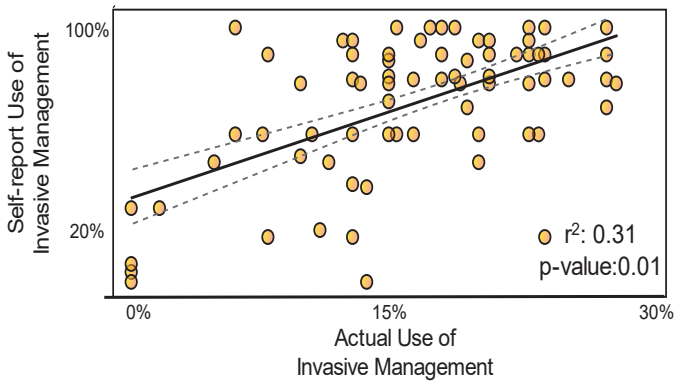

Figure 2: Correlation between observed and physician estimated rates of invasive management use in ACS patients.

2.2.2.Patient complexity: Several analyses have observed lower rates of evidence-based therapy use among higher risk groups.(2-4) Dissecting this relationship further, a strong relationship between the use of evidence-based therapies and increased myocardial risk (either ECG or biomarker abnormalities or haemodynamic compromise), but a strong negative correlation between guideline use and the presence of co-morbid medical conditions, such as renal impairment, chronic lung disease, prior heart failure, cerebrovascular disease and advanced age has also been demonstrated.(5) Integrating evidence into patient complexity is challenging. When patients "fit the evidence" guideline care is more frequently applied, but when they do not, uncertainty in applying the evidence persists. It is sobering to recognize that ~2% of patients contribute to the clinical trial evidence base, while clinical trials often actively exclude patients with significant co-morbidities.(6) *A greater capacity for risk stratification and support in weighing of risk and benefit may assist both cardiovascular and non-cardiovascular specialists to extend the current evidence-base to greater proportion of patients and potentially further improve outcomes.*

2.2.3. Misperceptions of patient risk impacts practice and outcome.

A study of physician perception of risk compared with objective risk stratification provided by the GRACE risk score among 1542 ACS patients in Australia, China, India and Russia has recently been completed. For each specific patient, 2 or 3 physicians (81% with a cardiovascular specialist qualification, median time from medical qualification: 10 years) directly involved in the patients care were asked to assess the patients "untreated" risk of death by 6 months and then determine the value of the impact of current guideline recommended therapies. (PREDICT study: Accepted Circ. CV Outcomes and Quality 2013) Compared with the GRACE risk score, physicians generally over-estimated low risk patients and under-estimated high risk patients. Consequently, the GRACE risk score was superior to physician estimation of 6-month mortality (C-statistic: GRACE score: 0.81 versus Physician Estimation: 0.65, P<0.001).

Adding the GRACE score to physician estimation increased risk discrimination (Integrated Discrimination Index (S.E.): 0.063 (0.012), p<0.001). Furthermore, when care was correlated with physician perception of risk, percutaneous coronary intervention (PCI) rates were higher among those at increased risk (Figure 3). In contrast, when care was correlated with objectively measured risk using the GRACE risk score, lower PCI rates among high-risk patients was evident. By 6-months, mortality rates were higher among patients in whom the risk was underestimated. (Not under-estimated: 10/967 (1.0%) vs. one physician underestimated: 25/429 (5.8%) vs. all physician's underestimated: 13/146 (8.9%). After adjusting for GRACE risk and frailty, any physician underestimation of risk was associated with a 6.0 fold increase in 6-month mortality (95% C.I.: 2.3-15.5, p<0.001). (PREDICT study: Personal Communication). It is intuitive that improving physician application of risk stratification will improve outcomes, however this hypothesis, which is derived from these observational data, needs to be prospectively tested.

2.2.4 Contextual factors that facilitate care: Hospital level processes for implementing guidelines such as protocols, knowledge resources and workforce characteristics have often evolved without evaluation of their impact on outcomes. The specific system-based decision tools such as the formal implementation of objective risk stratification designed to facilitate guideline application and better outcomes warrant closer exploration. Evaluation of the system-based components of ACS care among 35 Australian hospitals has observed heterogeneity in the implementation of quality improvement tools with poor correlation between these strategies and outcomes.(7)However, those patients treated in a hospital with an electronic process for ensuring evidence-based application experienced a 51% reduction (Odds ratio 0.49, C.I. 95% CI; 0.35-0.68, p <0.001) in 12-month mortality.(7)*Active design of clinical processes conducive to the delivery of evidence-based care may represent an opportunity to improve clinical outcomes.*

2.3 Objective risk assessment in ACS: the GRACE risk score

The GRACE risk score is a set of clinical risk stratification indices developed from >100,000 patients enrolled from 247 hospitals in 30 countries.(8,9) Using age, haemodynamics, ECG changes, cardiac marker elevation and renal function, this objective assessment of risk has been validated in several dataset including several Australian cohorts including ACACIA,CONCORDANCE and PREDICT, C-statistic 0.81).(10) In a recent study, the admission GRACE risk score identified those patients who benefitted from early angiography and revascularization (<48 hours). (11) Importantly however, the prospective routine application of a risk score into clinical decision making has not been shown to result in improved outcomes in the broader cohort of ACS patients. Despite this, its routine use has been advocated in the current American and European as well the

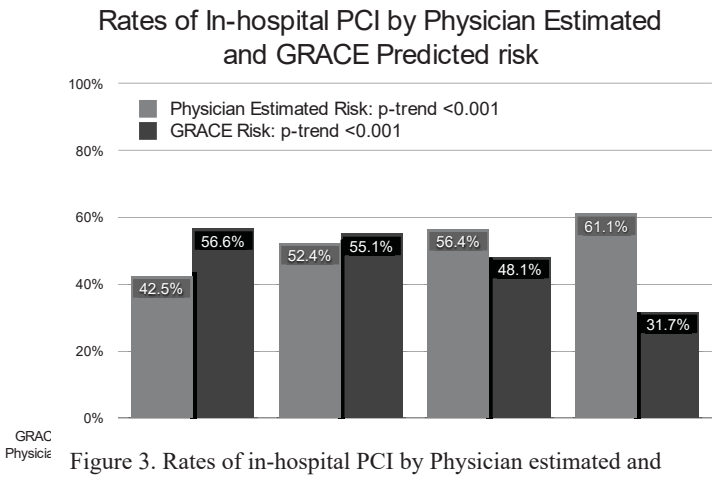

Figure 3. Rates of in-hospital PCI by Physician estimated and GRACE predicted risk

Australian and New Zealand ACS guidelines (e. Class IB indication in ESC Guidelines for management of NSTEACS). (11-14) The use of the risk tool at the bedside is limited, in part due to poor awareness of how it may influence clinical decision-making and, a strong reliance on doctor estimated risk. *Clinical equipoise regarding the utility of the GRACE risk score in ACS management remains, and the limited utilization provides an opportunity to evaluate the impact of routine application on clinical practice and outcomes.*

Other risk scores: Other risk scores for the prediction of ischaemic and bleeding risk have also been developed. These include the Thrombolysis in Myocardial Infarction (TIMI) risk scores for ST elevation MI (STEMI) and non-ST elevation ACS (NSTEACS), as well as the ACUITY and CRUSADE risk scores for the prediction of major bleeding events.(15-18) For ischaemic events, the TIMI risk scores, which have been derived from clinical trial populations, are also superior to clinical perception but appear inferior to the GRACE risk score. However, the prediction of bleeding events by the ACUITY and CRUSADE scores is poor as is physician perception. (PREDICT study: Accepted Circ. CV Outcomes and Quality 2013).

2.4 Translation Research: From National Agenda to Local Practice

2.4.1 The optimal application of current ACS evidence-based care is expected to provide greater survival gains than further innovation in any specific therapy. In an analysis drawn from contemporary Australian ACS practice and randomised clinical trial (RCT evidence), an system-wide approach aiming to provide a 25% increase in guideline adherence to the entire population has the potential to save 82 lives per 10,000 presentations with direct cost saving of > $300 million to the Australian community per year.(19) In contrast, since relatively few patients receive complete care, a novel therapy providing the same 25% mortality reduction among those already receiving all guideline recommendations would save only 5 lives saved per 10,000 presentations.(19) *These observations define the need for strategies that improve decision making to drive evidence to outcome for all ACS patients.*(20)

3. RESEARCH HYPOTHESIS

Objective risk stratification using the GRACE Risk Tool and treatment recommendation plan improves the achievement of hospital-level performance measures, and secondarily, provides a cost-effective approach to improving ACS outcomes.

Rationale for conducting this study

The interaction between health care provider and patient remains at the core of efforts to translate evidence to outcome. In part, modern sophisticated ACS care has relied on expert clinical intuition together with responsive integrated health care delivery for the timely provision of optimal care. ***Refining risk-based decision-making to reduce access inequities in rural, outer metropolitan communities due to limited expert care, while informing "misperceptions" of risk that lead to under-treatment of high-risk patients in metropolitan hospitals are the essential objectives of this proposal.*** Such innovations would also have significant relevance in countries where access to expert care is hampered by geographic distance such as Australia, or where the workforce capacity is challenged by the burden of care resulting from the urbanization of developing economies.

Contemporary data indicate under-utilization of early invasive management and proven pharmaco-therapies in ACS care. Approximately 1 in 2-3 patients will die, suffer recurrent MI or require readmission by 1 year after admission for MI. Effective ACS management requires rapid and accurate risk assessment and the timely delivery of resource intensive therapies. Faced with increasing patient complexity, where relative risks and benefits are often more difficult to weigh, it is not surprising that current care remains sub-optimal. An intervention providing contextual evidence-based decision-support support directly at the point of care may be a step forward in improving clinical outcomes by improving clinical guideline adherence and reducing inequities in health care provision through the support of clinical capacity in rural areas. However, the validity of this strategy is unproven and should be tested within a robust randomized comparison. Understanding the relative impact of this approach will inform current efforts to minimize the heterogeneity in ACS care through the use of evidence-based decision support, not only in ACS care but also across the broader emerging Health agenda.

a. Benefit/risk and ethical assessment

This study is assessing a practice-level intervention directed at acute hospital care. Current evidence suggests that under-appreciation of risk is prevalent and is associated with reduced access to care and worse clinical outcomes. The anticipated benefit to patients cared for in hospitals randomised to risk stratification using the GRACE risk tool and treatment recommendation plan, is that the new protocol may be associated with improved adherence to evidence-based care and clinical outcomes. However, there remains a risk that patients cared for in hospitals randomised to the risk stratification tool and treatment recommendation plan will have an increased incidence of procedure or drug related complications without an improvement in outcomes. Consistent with this, one study has shown that electronic decision support in the intensive care environment has been associated with an increase in morbidity and mortality.(21, 22) Hence, equipoise regarding the study question remains. This study will employ a Data Safety Monitoring Committee to monitor the progress of the study.

4. STUDY OBJECTIVES

This study seeks to enhance evidence-based decision-making and objective delivery of acute coronary syndromes (ACS) care by evaluating the benefit of risk stratifying ACS patients using the GRACE

Risk tool and treatment recommendation plan versus standard care in a hospital-level cluster-randomised clinical trial design.

a. Primary objective

Evaluate the effectiveness of risk stratification using the GRACE Risk tool and treatment recommendation plan for ACS patients on the in-hospital use of evidence-base investigations and therapies and secondary prevention assessed at the time of discharge.

b. Secondary objectives

1. Determine the incremental net clinical benefit and cost-effectiveness of risk stratification using the GRACE Risk tool and treatment recommendation plan on care within the routine clinical environment;
2. Determine the incremental net clinical benefit of risk stratification using the GRACE Risk tool and treatment recommendation plan on the reduction of cardiovascular death, myocardial infarction, new or worsening heart failure, and cardiovascular readmissions at 12 months.

This study will be conducted as part of an international network of cluster-randomised studies evaluating risk stratification using the GRACE Risk tool and treatment recommendation plan within the United Kingdom, Canada, and the Asian region, and will contribute to a planned meta-analysis of these studies evaluating the impact on death or recurrent myocardial infarction.

c. Exploratory objectives

1. To correlate clinical performance measured by established performance indicators in ACS with 12-month clinical outcomes;
2. To explore the health service characteristics associated with higher and lower performance on ACS clinical performance indicators and the interaction with risk stratification using the GRACE Risk tool and treatment recommendation plan.

5. STUDY PLAN AND PROCEDURES

a. Overall study design and flow chart

To evaluate the effectiveness of objective risk stratification using the GRACE Risk tool and treatment recommendation plan versus standard care for improving the use of evidence-based investigations, therapies and secondary prevention in hospital. A cluster-randomised implementation trial with blinded endpoint evaluation for clinical events recorded in-hospital and during the follow-up period will be used. (Figure 4: Cluster randomized design of GRACE risk score versus standard care study schematic).

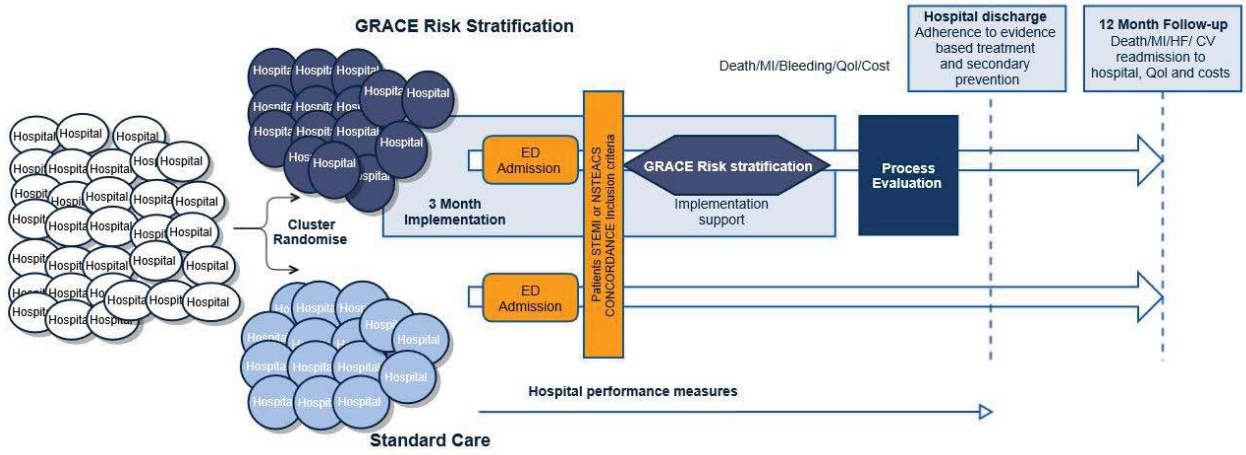

Figure 4: Cluster randomised design of GRACE risk score versus standard care

b. Rationale for study design

Given that clinical care among patients within hospitals is correlated and the intervention is system-based, randomisation and the implementation of the GRACE Risk tool and treatment recommendation plan will be required to prevent between clinician contamination. Since the system-level intervention directed at supporting decision-making is under investigation, blinding of the intervention is not appropriate. Hence, this study will employ a prospective randomised open-label blinded endpoint (PROBE) design and employ a blinded event adjudication committee, relying on objective measures of hospital performance and clinical events. Furthermore, to avoid selection bias occurring within each hospital site, consecutive enrollment of all eligible patients admitted to the site within the enrolment period will be sought using an "opt-out consent" process.

6. HOSPITAL AND PATIENT SELECTION CRITERIA

a. Hospital-level Inclusion criteria

Public Hospitals from metropolitan and regional/rural centres that fulfill the following characteristics will be eligible to participate:

- The presence of an onsite 24/7 emergency service.
- ED, Cardiology/medicine services willing to implement the GRACE Risk tool and treatment recommendation plan into their care process.

Hospitals will be stratified by size of hospital and hospital performance in key process measures. (23) Randomisation will reflect equal representation of hospitals across each stratified tier in both arms of the study.

Hospitals with an existing implemented risk stratification support system for the management of ACS patients will be excluded.

b. Patient-level Inclusion criteria

Patients are eligible if they present to hospital with symptoms felt to be consistent with acute cardiac ischaemia for >10mins within 24 hours of presentation to hospital **plus** one of the following: ECG changes; elevated enzymes; documentation of CAD or documentation of 2 or more features of high risk ACS.

ECG changes:

- transient ST segment elevation of 0.5mm in two or more contiguous leads;
- ST segment depression of 0.5mm in two or more contiguous leads
- new T wave inversion of 1 mm in two or more contiguous leads
- new Q waves (1/3 height of R wave or >0.04 seconds)
- new R wave > S wave in lead V1 (posterior MI)
- new left bundle branch block

Increase in cardiac enzymes:

- increase in troponin T above the upper limit of normal;
- increase in troponin I above the upper limit of normal;
- CK-MB 2x upper limit of the hospitals normal range **or** if there is no CK-MB available, then total CK greater than the upper limit of normal.

Documentation of Coronary Artery Disease:

- history of MI, angina, congestive cardiac failure due to ischaemia or resuscitated sudden cardiac death;
- history of, or new positive stress test with or without imaging;
- prior or new, cardiac catheterisation documenting coronary artery disease;

- prior, or new percutaneous coronary artery intervention or coronary artery bypass graft surgery.

At least 2 of the following High Risk features:

- haemodynamic compromise (BP<90 and HR >100)
- left ventricular systolic dysfunction (LVEF<0.40);
- presence of known diabetes
- documentation of chronic kidney disease (estimated GFR <60mls/min)

Permission to include ACS patients who meet the above inclusion criteria but die before the opt-out consent process will be included using a waiver of the opt-out process. Approval will be sought from each local Human Research Ethics Committee

Exclusion criteria

Patients presenting to hospital with an ACS accompanied with, or precipitate by significant co-morbidity e.g. motor vehicle accident, trauma, severe gastrointestinal bleeding, peri-operative or peri-procedural MI will be excluded. Patients already recruited into the study cannot be re-enrolled into the study.

7. HOSPITAL RANDOMISATION AND SUBJECT ENROLLMENT

a. Procedures for Hospital randomisation to the GRACE Risk tool and treatment plan

Cluster randomisation will be undertaken at the level of the hospital (1:1, GRACE Risk tool and treatment recommendation plan versus usual care). An independent statistician will use a table of random numbers to assign half the hospitals to the intervention ensuring that hospitals across each stratified tier will be represented in both arms of the study. The concealed randomised allocation will be revealed to the hospital only after all ethical and research governance documentation has been completed and the site is ready to initiate the study.

b. The GRACE Risk tool and treatment plan

1. **Risk stratification using the GRACE risk tool and treatment recommendation plan.** The GRACE risk tool and treatment recommendation plan is a patient-level clinical risk stratification worksheet with simple treatment recommendations applied within those hospitals randomised to the active arm. The tool will be implemented through either a paper-based worksheet or electronic medical records within the hospital at the earliest time-point of the patient's admission to hospital. After assessment of basic clinical data including symptoms, clinical findings, past-history, ECG changes, biomarker elevation and basic biochemistry, the calculation of the GRACE Risk tool to predict in-hospital and 6-month mortality risk in all patients will be required.(9,10,24) Simple dichotomous management recommendations with respect to use and timing of early angiography and possible revascularization as well as anti-thrombotic therapies consistent with the NICE guidance, secondary prevention therapies and referral to cardiac rehabilitation will be made.(11,25)

Data, including all baseline measures and clinical assessments, therapies and timing of treatments, will be recorded in the electronic CONCORDANCE Registry case report form.

The worksheet will consist of the following risk stratification calculators, nomograms and clinical orders:

i. Ischaemic risk:

The ischaemic risk calculator will list key clinical information required to generate the latest version of the GRACE risk score available, and will provide the clinician with a numeric risk estimate for death and the composite of death or new/recurrent MI by 6-months.

ii. Bleeding risk:

An estimate of bleeding risk will also be provided using an internationally accepted bleeding risk scale.

iii. Nomograms:

Nomograms for the quantification of risk and benefits: will provide patient-specific incremental reductions in recurrent events using literature-based estimates of treatment effect associated with invasive management and secondary prevention therapies. A nomogram detailing the expected patient-specific risk of major bleeding events combined with recommendations associated with radial angiography, and use of antithrombotic therapy will also be provided. These will assist clinicians in deciding on the use of invasive management and facilitate communications with patients and families by providing the individualized expected absolute risk and expected benefits associated with specific guideline recommended

iv. Treatment recommendation plan:

Specific recommendations based on threshold values of the GRACE risks score or guideline recommended care will also be provided. A sample of the implementation tool is included (see Appendix…) In order to maximise uptake it will be permissible for sites randomised to the GRACE risk tool and implementation plan to modify both the layout of the tool, and the specific recommendations for inclusion in the tool to reflect local practice. Local changes will be approved by the Steering Committee who will ensure that these recommendations include the process measures that comprise the primary endpoint of the AGRIS study (ie coronary angiography, secondary prevention drugs and rehabilitation for high risk patients).

vi. Clinical orders:

The worksheet will include a section to enable the admitting clinician to document the intended therapies including prescription of acute and long-term guideline recommended therapies, specifying the need for and planned timing of invasive management, and referral to secondary prevention services. The ability to record whether each of these therapies is "indicated," "not-indicated" and "contra-indicated will also be included on the worksheet.

Where possible, it will be deployed at each hospital at the earliest time-point following admission to hospital. This worksheet will also serve as the source document for part of the case-report form for each participant of the study,

2) Standard care: Hospitals randomised to standard care will continue to approach and enroll consecutive ACS patients into the CONCORDANCE Registry using the opt-out consent process. Data, including all baseline measures and clinical assessments, therapies and timing of treatments, will be recorded in the electronic CONCORDANCE Registry case report form.

c. Implementation of the GRACE risk tool

The GRACE risk tool treatment recommendation plan will be embedded within the routine clinical assessment and management procedures at each of the hospitals randomised to the active arm. A 3-month implementation period will be followed by the active recruitment period (estimated 9-12 months).

Integration of the Grace Risk tool into the clinical workflow will require significant clinical leadership from local medical and nursing champions. Study resourced implementation experts will assist with this process. The engagement of local leaders will be necessary to a) appropriately influence and modify the admission documentation and clinical processes including identifying which specific local staff member is responsible for completion of the form (i.e. cardiac resident, or nursing) and b) facilitate communication regarding the relevance and utility of objective risk stratification to each component of the ACS team facilitating adherence to the new processes.

During the implementation period, an external trainer will work closely with the study site (i.e. local clinical lead, medical, nursing and allied health staff) to facilitate the incorporation of the risk assessment worksheet into current work practices, including the use of paper documentation, other risk calculators, and treatment protocols. The time and resources required in implementation will be included in the cost-effectiveness analysis.

The roles at of the external trainer and the implementation team at each hospital is separate to that of the clinical trial coordinator whose responsibilities are for the operational and regulatory aspects of the study including obtaining ethical and governance approval for the conduction of the study patient recruitment, management of the Grace Risk tool worksheet, data entry in the electronic CRF and reporting of clinical events.

Differentiation between the Grace Risk tool and treatment recommendation plan and usual care will be critical to the scientific integrity of this study. As a consequence, efforts will be made to ensure the consistent uptake of the intervention at the hospitals randomised to the active arm. Facilitating the completion and clinical influence of the GRACE risk tool may require several levels of engagement. While the specific characteristics of the implementation will vary between hospitals, the following principles will apply:

- Adjustment of the admission process to include risk stratification with the GRACE risk tool
- Communication on the clinical utility and relevance of the GRACE risk tool to the entire multi-disciplinary team, specific to their roles.

Calculation and documentation of the GRACE risk score will be completed by the medical officer completing the patient's admission or the senior clinical nurse depending on local circumstances and will be reviewed by a more senior medical clinician (i.e. medical registrar, cardiology registrar, consultant) where possible.

Efforts to extend the relevance of the GRS intervention to other disciplines within the acute care team (including nursing, pharmacy and cardiac rehabilitation) recognises significant variation in the levels of engagement, autonomy and authority to initiate care across hospitals. Consequently, a single standardised information session informing these disciplines of the potential value of the GRS intervention to their workflow will be undertaken early during the implementation phase.

d. Documentation of the GRACE Risk Score

The GRACE Risk tool will be provided to sites in paper form or incorporated into the electronic medical records if required and will be copied and collected as a source document to assess how it is applied in the clinical environment. The original form will remain in the patient medical record and uploaded into the patient care system where possible.

8. COLLECTION OF STUDY VARIABLES

a. Recording of data

Clinical data will be recorded on a web-based clinical record file (CRF) developed for the CONCORDANCE Registry.

b. Data collection at enrolment and follow-up

The GRACE Risk tool and treatment recommendation plan will be developed by a committee of experts in the treatment of patients with ACS and the systems and processes of care that apply in accordance with best practice evidence from clinical trials and guidelines where they exist.

Baseline Data

Baseline data will include demographic factors, cardiac risk factors, frailty index, current and past medical diagnoses and their timing, time to presentation, clinical risk stratification parameters and clinical parameters reflecting processes of care as documented in the electronic and paper based medical record.

A more detailed survey for hospital and local barriers to implementation will be evaluated in a qualitative manner. These data will include;

- Geographical location, and whether rural or metropolitan
- Hospital type (academic/teaching; public; private)
- Total number of hospital beds
- What size population the hospital serves
- Number of ACS admissions per year
- Hospital facilities (Coronary Care Unit; Open Heart Surgery Theatre; number of cardiologists; number of interventional cardiologists; number of catheterisation laboratories, number of cardiac surgeons).
- Number of Coronary Angiograms performed per year
- Number of Primary PCI performed per year
- If the enrolling hospital does not have an onsite cath Lab, the name of the hospital where patients are referred to for interventional procedures
- Distance from enrolment hospital to hospital with interventional cath-lab facilities
- Presence of quality improvement staff

Follow-up procedures

Participants will be followed up at 12 months from the date of hospital discharge. Follow up visits may be performed via telephone, patient letter, General Practitioner contact, next of kin contact and/or hospital admission data base. If no participant data is available at the 12-month time point, the participant's name will be checked against the National Death Index for mortality status to ensure that all participants have an outcome listed at 12 months. If vital status is unable to be confirmed via the above methods including National Death Index or any other administrative registry if available, patients will be removed from the final analysis.

Late clinical evaluations (hospital discharge to final study visit) will be conducted by study coordinators and supplemented by hospital records and the National Death Index. Quality of life measures, using the 5-level EQ5D instrument, will also occur at 1 year.

c. Enrolment procedures and the opt-out consent process

The physician or study coordinator will check if the patient fulfils the inclusion and exclusion criteria. Hospital admission records will be used to generate screening logs to assist in the identification of eligible patients. Since this is a hospital level intervention and in order to avoid biased sampling of the ACS population patients are enrolled via an opt-out consent process.

Patients will receive an information sheet in lay-man's language. The patient, their relative or carer will be provided with the opt-out consent form detailing; why their data is being collected and how it will be used; what data will be collected ie; their identity and some clinical information; how their data may be linked and shared; details on how to opt-out of the study and the name and the phone number of the person to notify and the contact details of the hospital. Assurances will be made that they are able to opt-out at a later date and that the decision not to participate in the study will not affect their medical treatment or their relationship with the staff that are caring for them. They will also be given details on how to lodge a complaint through an independent complaints process.

In order to ensure the study is representative of all ACS patients, it is important to include the sub-set of patients who die early during their admission to hospital. Consent waivers will be sought for patients who die during their admission or are too ill to provide consent. This waiver ensures that sites are able to enroll consecutively and truly reflect the ACS population presenting to hospital. The approval for this will be determined by each site's governing ethics committee. For patients who lack the competence to provide consent, or where the patient is from a Non-English speaking background and has limited command of English hospital staff will approach a person with lawful authority on behalf of that patient (this is usually the next of kin or carer) with the opt-out information sheet for the study.

The opt-out consent process meets the guidelines for the collection of identifiable information as outlined within Australian Commission on Safety and Quality in Health Care (ACSQHC) report on development of operating standards for Australian Clinical Quality Registries (NEHTA) and the National Statement on Ethical Conduct in Human Research [1] [2] and Guidelines approved under Sections 95 and 95A of the Privacy Act 1988.

Patients are free to withdraw from this study at any time point during the course of the study. Upon withdrawal, the patient's data collected to that point will be included in the primary analyses unless the patient stipulates otherwise. No additional follow-up will be conducted.

d. Consent for data linkage to the Medicare and Pharmaceutical Benefits Schedules

In a subset of patients the physician/study coordinator will also obtain signed patient consent to access data from the Pharmaceutical Benefits Scheme (PBS) and Medicare Benefits Scheme (MBS). Patients will be informed how their data may be linked and shared and the type of data that will be collected. Theis data will contribute to the cost-effectiveness analysis.

e. Effectiveness

Clinical events will be identified through patient contact, and electronic and manual searches of hospital records, general practice notes and the National Death Index where possible. Where suspected events have been identified, source documents (described below) will be required to enable centralised clinical event adjudication.

f. Primary Outcome: Composite of ACS performance measures by hospital discharge:

The primary (hospital performance measure) endpoint will be the composite endpoint of adherence to the following performance measures by the time of discharge among those patients discharged alive:

i. Receipt of invasive or CT inpatient angiography during the index hospitalization where the patients GRS is >118.
ii. Prescription of at least 4 of the 5 clinical guideline advocated therapies drug classes at discharge if there is no stated contraindicated (patients with a stated contraindication will be coded as compliant). Specifically:
    (a) Aspirin≥100mg/day;
    (b) A beta-blocker;
    (c) A $P2Y_{12}$ inhibitor;
    (d) An ACE-Inhibition or ARB at discharge where is a history of hypertension, diabetes or known LV impairment (EF documented to be <50% by any form of cardiac imaging);
    (e) A HMG-CoA reductase inhibitor;
iii. Documentation of referral to cardiac rehabilitation services

Each of the criteria will be evaluated separately and aggregated to a possible score of 3 (i.e. 1 for inpatient angiography, 1 for at least 4 of the 5 secondary prevention pharmacotherapies, and 1 for referral to a secondary prevention program).

g. Secondary outcomes: Composite endpoint of cardiovascular death, new or recurrent myocardial infarction, new or worsening heart failure or cardiovascular readmission at 12 months

1. The secondary outcome is a clinical endpoint evaluated as the composite endpoint of cardiovascular death, new or recurrent myocardial infarction, in-hospital heart failure or cardiovascular readmission at 12 months defined as:

i. cardiovascular mortality
ii. New or recurrent MI defined as chest pain/discomfort associated with a rise and fall in cardiac biomarkers, or a new myocardial defect on echocardiography, and consistent with the new Universal Definition.(26)
iii. Development of new or worsening heart failure in hospital as evidenced by a deterioration in the Killip Class.

iv. Hospital admission for: unplanned coronary revascularization (non-elective PCI or CABG); cerebrovascular accidents with cerebral imaging; cardiac arrhythmias; CCF without MI; or unstable angina.

2. Cost-effectiveness evaluation

i. Health-related quality of life and associated utility estimated with the Assessment of Quality of Life (EQ5D) instrument at 1 year.(27)
ii. Resource use and cost over 12 months, including Medicare data in consenting patients (GP contact using Medical Benefits Schedule (MBS), medication use from Pharmaceutical Benefits Schedule (PBS) and in-patient admissions from the AN-Diagnosis Related Group (DRG) in participating hospitals.

The Investigator at each site is responsible for ensuring all local regulatory requirements and obligations relating to safety reporting to the Therapeutic Goods Administration following a serious adverse event that occurred following administration of a therapeutic drug during the study.

h. Patient reported outcomes (PRO)

Quality of life measures using the 5-level Euro-QoL 5D (EQ-5D) instruments, adherence to medical therapies, readmission to hospital with heart disease, planned and unplanned cardiovascular procedures, new or worsening heart failure and survival status will be collected via patient self -report 1 year. The EQ-5D is a standardised measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of health care as well as in population health surveys. EQ-5D is suited for use in postal surveys, in clinics, and in face-to-face interviews. It is cognitively undemanding, taking only a few minutes to complete.

i. Health economics

Patient level measures of utility derived from the EQ5D instrument will be integrated with survival curves to estimate quality adjusted life years in each trial arm using the quality-adjusted survival analysis (QASA) method.(28) Within-trial incremental costs associated with the GRACE risk tool and treatment recommendation plan and with standard care will be estimated from patient data on MBS, PBS and hospital use. Within-trial cost-effectiveness will then be analysed allowing for bivariate uncertainty with bootstrapping of patient costs and effects to maintain covariance structure. This analysis will include cost-effectiveness, acceptability, net benefit and expected net loss curves to inform decision makers of the optimal strategy at any given threshold, uncertainty around this decision and the potential value of further research locally and internationally.

j. Process evaluation

Semi-structured interviews with health care providers will be conducted in hospitals whose ability to implement the GRACE Risk tool and treatment recommendation plan is variable. Participants will include health care providers participating in the implementation process. A number of patient/hospital/system-level factors impact on a hospital's performance and identification of these factors and the degree to which they operate in each hospital is central to understanding why some patients receive care which is not in line with current management guidelines.

9. ETHICAL AND REGULATORY REQUIREMENTS

a. Ethics and regulatory review

Approval will be sought from each participating centre's Human Research Ethics Committee (HREC) and/or Governance Officer as required. Participation of medical practitioners, hospitals and patients in the study will be voluntary and approval from the local department and hospital executive will be required.

This study will be registered with Australian and New Zealand Clinical Trial Registry (www.anzctr.org.au).

b. The PBS and MBS Consent Process

Enrolment into the study will be via an opt-out consent process for main study. All patients will be informed of their right to withdraw from the study at any time without prejudice to their medical and/or nursing care at that time or in the future. Approval for to include and access the medical records of patients who meet the inclusion criteria but die before the opt-out information sheet is provided will be sought from the local hospital ethics committees.

Where possible, a subset of patients will be approached during their hospital admission and asked to sign the consent forms for access to data via the PBS and MBS in addition to linkage with the national hospital morbidity and mortality dataset. In order to ensure there is no impact on consecutive recruitment into the AGRIS study, patients may be consented for PBS, MBS and data linkage after recruitment into the study, that is at a later stage during their admission.

c. Data quality audits

The participating physician agrees to allow the /coordinating centre auditors to have direct access to his/her study records for review. It is understood that these personnel are bound by

professional secrecy, and as such will not disclose any personal identity or personal medical information.The participating physician will make every effort to help with the performance of the data quality audits and inspections, giving access to all necessary facilities, data, and documents.

The confidentiality of the data verified and the protection of the patients will be respected during these inspections. Any result and information arising from the inspections by the competent authorities will be immediately communicated by the participating physician to the Sponsor and Coordinating centre. The participating physician shall take appropriate measures required by the coordinating centre to take corrective actions for all problems found during the audit or inspections.

Appropriate measures will be taken to ensure the security of personal data (including storage of paper records in locked cupboards/filing cabinets, restricted access to computer databases and separation of personal identifying data from the participant records). All assessment data sheets and files will contain subject ID only. The study database will be retained indefinitely at Centre for Outcomes Research (COR) at The University of Massachusetts Medical School, Worster.

10. STUDY ORGANISATION

The study will be conducted by the Sydney Local Health district Concord Hospital and the Steering Committee is co-chaired by the PIs Professor David Brieger and Professor Derek Chew and includes the CIs and the Project Manager (PM). The Steering Committee has representation by senior cardiologists clinicians and statisticians from SLHD, Sydney University, the Cardiovascular Division of The George Institute for Global Health Sydney, the South Australian Health and Medical Research Institute (SAHMRI) and the University of Adelaide, SA. The Steering Committee is responsible for all aspects of the study design and implementation. It approves the final protocol, supervises enrolment and responds to the study management group, the data safety and monitoring board and clinical event adjudication committee. Analysis and manuscripts will be the responsibility of the Co-Chairs, CI's and PM. The PM and PI will produce half yearly and final reports.

The Steering Committee members include:

- Professor Derek Chew Co-Chair (Flinders University and Flinders Research Group Adelaide, South Australia)
- Professor David Brieger Co-Chair (Concord Hospital SLHD and Sydney University)
- Professor Anushka Patel (Chief scientific officer, The George Institute for International Health)
- A/Prof Graham Hillis (Co-Director Cardiovascular Division of The George Institute for International Health, Sydney)
- A/Prof Clara Chow (Cardiovascular Division of The George Institute for International Health, Sydney)
- Professor Laurent Billot (Senior Statistician at The George Institute for International Health, Sydney)

- Ms Bernadette Aliprandi-Costa (Senior Project Manager Concord Hospital SLHD and Sydney University)
- Dr Carolyn Astley (Flinders Research Group Adelaide, South Australia)
- Dr Steve Quinn (Senior Statistician, Flinders Clinical Effectiveness, Flinders University)
- A/Professor Donna Waters (Associate Dean, Research) Faculty of Nursing, Sydney University
- Health Economist: To be appointed

This committee is comprised of experts in the field of cardiology and the conduct of observational outcomes research. They will be responsible for scientific advice and recommendations on the:

- Scientific integrity of the registry
- Protocol and CRF
- Methodology to obtain the most representative population of participants and ensure good long term data quality;
- Implementation of the GRACE risk tool and treatment recommendation plan and process evaluation;
- Development of the overall operational guidelines for communication and publication;
- Collation of event reports to be assessed by the event adjudication committee;
- Governance over the academic analyses and publications derived from the protocol;
- Conduct of the Statistical analysis and the writing of the primary manuscript.

The committee will follow the status of the study by regular face to face meetings or teleconference during the registry.

Data management services will be provided by the Centre for Outcomes research (COR) at The University of Massachusetts Medical School, Worster MA USA. Data management will be responsible for data programming, query tracking and resolution, The COR web site is hosted within the secure UMMS Information Service environment that also houses statistical and graphics software. The front-end user-friendly interfaces use ASP.NET to support data storage and retrieval from the back-end SQL server database. Standards for HIPAA compliance include HTTPS protocol, 128 bit encryption, and individual Web login account. Data are organised in a structured format, and produce surveillance reports using query, search and analysis functions. Export features allow data to be extracted, in whole or in part, using Text, Excel and XML formats for further statistical analysis by the Steering Committee.

Coordination of the clinical event adjudication (CEA) process will be conducted via an independent Committee located at SAHMRI and the data Safety Monitoring Board will be a separate independent committee appointed and located at SAHMRI.

Support for the implementation of the GRACE risk tool and treatment recommendation plan will be coordinated by SAHMRI in cooperation with members of the Steering Committee.

a. Roles and Responsibilities of the study coordination centre

Training of study site personnel is the specific responsibility of the Study Coordination Centre at SLHD Concord Hospital and includes, overseeing the financial and regulatory aspects of the study, development of the case report forms**,** development of training manuals and audit procedures**;** tracking of data completion**,** resolution of data queries and monitoring data quality, and to perform data analysis for scientific publications.

b. Roles and Responsibilities of the Implementation Team

Study-resourced implementation managers led by SAHMRI will be responsible for implementing the study at each site, education of clinical staff involved and ensuring adherence to protocol specifications. Clinical champions will also need to be identified in order to directly engage and ensure the support of local ED and cardiology department clinicians. The study implementation managers will work closely with the study site to merge the risk stratification tool within current work practices. The study team will conduct training sessions to inform local clinical staff and study co-coordinators regarding the use of the tool. Qualitative descriptions of the local barriers and solutions experienced during the implementation of the tool at each site will be recorded to inform future efforts in generalizing the findings of the study. Time and resources required for implementation will be included in the cost effectiveness analysis.

c. Roles and Responsibilities of the Process Evaluation Team

A study-resourced process evaluation team co-located at the University of Sydney and the University of Adelaide will be responsible for the qualitative evaluation of the effectiveness of the implementation process at purposively selected sites. The methodology for this qualitative evaluation and interview questions will be submitted for ethical approval separately to selected centres.

d. Data Management

The project and data management will be based at the The Center for Outcomes Research (COR) at the University of Massachusetts Medical School (UMMS). Information collected will include baseline patient demographic and presentation characteristics, in hospital investigations, medical management and in-hospital outcomes. Data will be are collected electronically. The data protection standards at COR, currently meet all standards relating to the use of paperless records under the Good Clinical Practice regulations and comply with US Federal Information Systems policies including uniform policies, authorities, responsibilities, and compliance for System Security Planning within UMMS. This policy also provides guidance for developing system security plans in accordance with National Institute of Standards and Technology (NIST) Special Publication (SP) 800-18, "Guide for Developing Security Plans for Federal Information System" and "NIST SP 800-53 The systems and procedures comply with the Electronic Records; Electronic Signatures; Final Rule: Electronic Submissions; Establishment of Public Docket; Notice of CRF 21 Part 11 of these regulations. Furthermore the systems and processes with respect to privacy and data protection comply with Health Records and Information Privacy Act (NSW) 2002 and Privacy Act (Cth)1988 and Australian Information Privacy Principles.

The COR web site is hosted within the secure UMMS Information Service environment that also houses statistical and graphics software. The front-end user-friendly interfaces use ASP.NET to support data storage and retrieval from the back-end SQL server database. Standards for HIPAA compliance include HTTPS protocol, 128 bit encryption, and individual Web login account. Data are organised in a structured format, and produce surveillance reports using query, search and analysis functions. Export features allow data to be extracted, in whole or in part, using Text, Excel and XML formats for further statistical analysis. The system is also compliant with the National E-Health Transition Authority (nehta) standard of reporting and storing data using a hierarchical structure of .pdf, XML and UML. These controls to maintain privacy and security of the data include measures designed to ensure the integrity of system operations and information stored in the system. Such measures include:

- Validation;
- COR generates accurate and complete copies of records;
- Archives and backs-up all records;
- Uses computer-generated, time-stamped audit trails;
- All staff who develop, maintain, or use electronic records and signature systems have the education, training, and experience to perform their assigned tasks.
- System access is limited to authorised individuals;
- Operational system checks are used to enforce permitted sequencing of steps and events
- Authority checks are used to ensure that only authorised individuals can use the system, electronically sign a record, access the operation or computer system input or output device, alter a record, or perform operations.

Checks are used to determine the validity of the source of data input or operation instruction; and written policies are established and adhered to holding individuals accountable and responsible for actions initiated under their electronic signatures, so as to deter record and signature falsification.

11. Clinical Event Adjudication Committee (CEAC) and Data and safety monitoring board (DSMB)

a. Clinical Event Adjudication Committee (CEAC)

The clinical endpoint adjudication committee (CEAC) will be chaired by a senior physician with extensive cardiac experience. All other committee members will be cardiology consultants or fellows. The committee will be independent of all study investigators, sites, and the project and data management groups.

Source data required to confirm an event will first be sent in a de-identified format to the CEAC coordinator based at Concord Hospital. The documentation will be reviewed for completeness before the allocation of an event-specific Clinical Endpoint number which will replace all patient and institution codes on each source document, for that event, before submission to the CEAC. This process will ensure the CEAC remains blinded to both patient and institution identifiers. All event review requests and associated documentation will be submitted to the CEAC via a password-protecting portal.

The CEAC will review the followingevents (as required for the meta analysis on the international network of cluster randomised studies) .and associated source documents according to the requirements of the protocol, study timelines and following study specific standard operating procedures (SOPs):

- All deaths during hospital admission and at 12 months post discharge.
- All new / recurrent Myocardial Infarctions (including spontaneous and peri-procedural)

Should any communication be required with the site (eg. a request for additional information), this will be conducted via the CEAC coordinator to the coordination centre staff at Concord Hospital and then site.

b. Data Safety Monitoring Board (DSMB)

Within the scope of the Data Safety and Monitoring Board (DSMB) charter, this committee will ensure that no increase in adverse events associated with risk stratification using the GRACE risk-score intervention is introduced. The DSMB will consist of members who are external to the study and the CEAC. The DSMB will be constituted by 3 senior clinicians from non-participating hospitals and one (non-voting) statistician and will be chaired by an independent cardiologist.

When 50% of anticipated patients have been enrolled, the adjudicated clinical events will be forwarded to the DSMB following re-identification of the treatment arm by the CEAC coordinator. The DSMB will review the data to compare the number and type of events in each group and report on the findings. These results will be advised to HREC's and participating sites following each review.

In the event that there is a disparity between the groups then the DSMB may make a recommendation regarding the continued conduct of the study. The DSMB is responsible for

safeguarding the interests of study participants, assessing the safety and efficacy of study procedures.

The DSMB reviews data generated by the study in a periodic basis and recommends one of the following actions to the Principal Investigator:

- Discontinue the study (with provision for orderly discontinuation in accord with good medical practice).
- Modify the study protocol. Modifications may include, but not limited to, changes in inclusion/exclusion criteria, frequency of patient follow up visits or safety monitoring, alterations in study procedures.
- Continue the study according to the protocol and any related amendments.

12. Ownership of the data and study results

Unless otherwise specified by local laws and regulations, the Sponsor (SLHD) together with the Steering Committee retains ownership of data, results, reports, findings, discoveries related to this study. Therefore, the Sponsor reserves the right to use the data from the present study for any purpose.

13. Publications

The final decision to publish any manuscript/abstract/presentation will be made by the Steering Committee.

All manuscript/abstract/presentation must be submitted to the Steering Committee for review at least forty-five (45) calendar days in advance of submission. Astra Zeneca may request that the Company's name and/or names of one or several of its employees appear or do not appear in such publication. This latter condition will be contingent upon the employee contributing sufficiently to the academic production of the manuscript as per the NHMRC publication guidelines for authorship.

14. Evaluation and calculation of variables

a. Clinical Characteristics during the index presentation

- Demographics (Initials,year of birth,and postcode gender**)**
- Medical history (angina; TIA/stroke; diabetes; Coronary Artery Disease; Myocardial Infarction; Percutaneous Coronary Intervention; Coronary Artery Bypass Grafting; positive stress test; Peripheral Arterial Disease; Atrial Fibrilliation; malignancy; major bleeding; renal failure; obstructive sleep apneoa), History of Depression
- Cardiovascular risk factors (previous cardiac history – from above; smoking status; hypertension; hyperlipidaemia; obesity; family history)
- Date and time of admission

- Date and time of symptom onset.
- Presenting clinical symptomatology
- Presumptive initial diagnosis
- Physician Predicted risk of ACS
- Serum cholesterol, creatinine, white cell count, haemoglobin, urinalysis (if performed by the hospital)
- In-patient therapies: procedures (echocardiography; exercise tolerance test; left ventricular ejection fraction; pacemaker; other)
- In-patient therapies: interventions (cardiac catheterisation; percutaneous coronary intervention; coronary artery bypass grafting; stenting; clinical trial; other)
- In-patient therapies: drug treatments (Thrombolytics – streptokinase, alteplase, reteplase, tenecteplase; Anti-Coagulants - unfractionated heparin, low molecular weight heparin, warfarin, dabigatran; Antiplatelets – GP IIb/IIIa, aspirin, $P2Y_{12}$ inhibition, unfractionated heparin, low molecular weight heparin, other; Other Medications – ACE inhibitor, angiotensin receptor blocker, calcium channel antagonist, beta blocker, statin, clinical trial, other)
- In-patient events (myocardial infarction – not as part of admitting reason; re-infarction; recurrent angina, congestive heart failure; cardiogenic shock; pulmonary oedema; acute renal failure; stroke – haemorrhagic and non-haemorrhagic; major bleeding; sustained ventricular tachycardia or ventricular fibrilliation)
- Medications at discharge (aspirin; warfarin; P_2Y12 inhibition; ticlopidine; ACE inhibitor; angiotensin receptor blocker; calcium channel antagonist; beta blocker; digoxin; diuretic; nitrate; statin; dabigitranm, rivaroxaban and apixaban; clinical trial; other)
- Place of discharge (home; transfer – acute care, rehabilitation, for procedure - specify, other)
- Date of discharge
- Primary discharge diagnosis (acute coronary syndromes; other cardiac diagnosis – specify; other).

b. Death and readmission for cardiovascular causes within 12 months

- Cardiovascular mortality
- Unplanned hospital admission for: non-elective coronary revascularization (PCI or CABG); cerebrovascular accidents with cerebral imaging; atrial or ventricular arrhythmias; (re) MI, CCF; as documented by a hospital discharge summary or diagnosis-related group report.
- Significant Bleeding
- Medications (aspirin; warfarin/other anti-coagulants; clopidogrel, prasugrel, ticagrelor; ACE inhibitor; angiotensin receptor blocker; calcium channel antagonist; beta blocker; digoxin; diuretic; nitrate; statin; clinical trial other)
- Receipt of secondary prevention
- Quality of life assessment

c. Quality of Life: EQ-5D Calculation or derivation of efficacy variable(s)

Quality of life measures using the EQ5D instrument will be collected at 1 year. Linkage to the PBS/MBS data and NHMMD will also be sought from consenting patients. Resource use from the date of enrolment up to and including 1 month beyond the final assessment will be costed using MBS, PBS and AN-DRG cost weights.

d. Definitions of outcome variables

i. Cardiovascular Death

Cardiovascular Death will be defined as death due to myocardial infarction, sudden cardiac death, death due to heart failure or cardiogenic shock, stroke, and other causes including pulmonary embolism, or aortic aneurysm rupture.

ii. Myocardial Infarction

This study will implement the Third Universal Definition of myocardial infarction.(26) The appropriate definition of myocardial infarction will depend upon the clinical situation for which it is being applied. However, given the complexity in diagnosing myocardial infarction soon after the index event, suspected recurrent myocardial infarction will only be sought 18 hours after the time to presentation.

New MI

A myocardial infarction with evidence of myocardial necrosis in a clinical setting consistent with myocardial ischaemia that includes one of the following

- Detection of a rise and/or fall of biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit (URL) together with the evidence of myocardial ischaemia with at least one of the following;
  - Symptoms of ischaemia
  - ECG changes indicative of new ischaemia, new ST-T changes or new LBBB
  - Development of pathological Q waves in the ECG
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
- Sudden unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischaemia, and accompanied by presumably new ST elevation, or new LBBB, and /or evidence of fresh thrombus by coronary angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.
- MI post PCI - see below MI post intervention
- MI post CABG - see below MI post intervention

Pathological findings of an acute myocardial infarction

Re-MI

The definition of an MI, in those not undergoing revascularization procedures will depend on whether or not the admission diagnosis is unstable angina or MI. Admission MI will be diagnosed if any troponin, CK-MB (or CK in the absence of CK-MB) determination is elevated >ULN within 12 hours of the most recent episode of chest pain that qualified the participant for the trial.

In participants without MI at admission, a MI after enrolment but prior to angiography will be diagnosed when:

- any elevation of troponin or CK-MB >ULN occurs (or CK >ULN in the absence of MB determination).

In participants with MI at presentation, in whom the elevated troponin or CK-MB (or CK) levels are documented to be falling or have returned to normal, diagnosis of a second infarction requires:

- a new elevation of troponin or CK-MB >ULN (or CK >ULN in the absence of MB determination) if the troponin or CK-MB (or CK) level has returned to <ULN, or
- a rise by >20% or 50% above the previous nadir level if the troponin or CK-MB (or CK) level, respectively, has not returned to <ULN.

In participants with MI at presentation, in whom the peak troponin or CK-MB (or CK) has not yet been reached, diagnosis of a second infarction requires:

(a) recurrent chest pain ≥30 minutes, or
(b) new ECG changes consistent with MI, and
(c) the next troponin or CK-MB (or CK) level measured approximately 8-12 hours after the event be elevated by at least 50% above the previous level.

iii. MI following PCI

Myocardial infarction associated with PCI requires an elevation of cTn values >5 x 99th percentile URL in patients with normal baseline values (>99th percentile URL) or a rise of cTn values >20% if the baseline values are elevated and are stable or falling.
In addition, either:

(i) Symptoms suggestive of myocardial ischemia, or (ii) new ischemic ECG changes or new LBBB, or
(ii) Angiographic loss of patency of a major coronary artery or a side branch or persistent slow- or no-flow or embolization, or
(iii) Imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.

Myocardial infarction associated with stent thrombosis is detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/ or fall of cardiac biomarkers values with at least one value above the 99th percentile URL.

iv. MI following CABG

In participants undergoing CABG, diagnosis of MI will require:

Myocardial infarction associated with CABG will require elevation of cardiac biomarker values >10 x 99th percentile URL in patients with normal baseline cTn values (>99th percentile URL). In addition, either

(i) New pathological Q waves or new LBBB, or
(ii) Angiographic documented new graft or new native coronary artery occlusion, or
(iii) Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

v. New or Worsening Heart Failure

New or worsening heart failure will be defined as the change of 1 or more in the patients Killip Class, between the presentation Killip Class and the worst Killip class documented for the patient during their hospitalisation.

- Killip Class I-Absence of rales over the lung fields and absence of S3
- Killip Class II-Rales over 50% of the lung fields and the presence of S3
- Killip Class III-Rales over more than 50% of the lung fields
- Killip Class IV- Cardiogenic shock

Medical record information may be also used to determine the worst Killip Class: cardiac failure is defined as symptoms of heart failure requiring diuretics and objective evidence or clinical evidence of heart failure including;

- Bibasilar rales in 50% or less of lung fields or an S3 heart sound (criteria is the same as Killip Class II)
- Pulmonary oedema (criteria as Killip Class III) as evidenced by a chest X-ray with pulmonary congestion
- Cardiogenic shock. This includes Hypotension (a systolic blood pressure of less than 90 mmHg for an extended period usually more than 30 mins; end-organ hypoperfusion (cool extremities or a urine output of less than 30 ml/h, and a heart rate of greater than or equal to 60 beats per minute).

vi. Significant Bleeding

Clinically significant bleeding will be defined as any one of the following:

- intracranial,
- retroperitoneal,
- intraocular,
- Gastrointestinal / genitourinary bleeding requiring intervention (endoscopy/transfusion) or cessation of therapies
- access site haemorrhage requiring radiological or surgical intervention,
- ≥5cm diameter haematoma at puncture site,
- reduction in haemoglobin concentration of > 4g/dL without an overt source of bleeding,
- reduction in haemoglobin concentration of > 3g/dL with an overt source of bleeding,

- re-operation for bleeding,
- use of any blood product transfusion,
- bleeding leading to re-hospitalization or prolongation of hospitalization

and meeting the bleeding classifications for TIMI Major/ minor/ minimal/ GUSTO/ ACUITY

- TIMI Major/minor/minimal bleed Major: Overt clinical bleeding (or documented intracranial or retroperitoneal haemorrhage) associated with a drop in haemoglobin of greater than 5g/dl (50g/l) or a haematocrit of greater than 15% (absolute).
- Minor: overt clinical bleeding associated with a fall in haemoglobin of 3g/dL to 5g/dL (50g/l) or a haematocrit of 9% to less than or equal to 15% (absolute).
- Minimal: Any clinically overt sign of haemorrhage (including imaging) that is associated with a <3 g/dl decrease in the haemoglobin concentration or <9% decrease in the haematocrit

GUSTO Bleeding Classification(29)

- Severe or life-threatening: Either intracranial haemorrhage or bleeding that causes haemodynamic compromise and requires intervention
- Moderate: Bleeding that requires blood transfusion but does not result in hemodynamic compromise
- Mild: Bleeding that does not meet criteria for either severe or moderate bleeding

ACUITY Bleeding Classification(30)

- Intracranial or intraocular
- Reduction in Hb of ≥ 4.0 g/dL without an overt source of bleeding, or of ≥ 3.0 g/dL with an overt source of bleeding
- Use of any blood product transfusion
- Haematoma ≥ 5cm in diameter, re-operation for bleeding, access site haemorrhage requiring intervention

BARC Bleeding Classification(31)

- Type 1: bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalisation, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional
- Type 2: any overt, actionable sign of hemorrhage (e.g, more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria: (1) requiring nonsurgical, medical intervention by a healthcare professional, (2) leading to hospitalisation or increased level of care, or (3) prompting evaluation
- Type 3:

  Type 3a
  1. Overt bleeding plus hemoglobin drop of 3 to <5 g/dL* (provided hemoglobin drop is related to bleed)
  2. Any transfusion with overt bleeding

  Type 3b
  1. Overt bleeding plus hemoglobin drop ≥5 g/dL* (provided hemoglobin drop is related to bleed)

2. Cardiac tamponade
3. Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid)
4. Bleeding requiring intravenous vasoactive agents

Type 3c

1. Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal)
2. Subcategories confirmed by autopsy or imaging or lumbar puncture
3. Intraocular bleed compromising vision

- Type 4: CABG-related bleeding
  1. Perioperative intracranial bleeding within 48 h
  2. Reoperation after closure of sternotomy for the purpose of controlling bleeding
  3. Transfusion of ≥5 U whole blood or packed red blood cells within a 48-h period†
  4. Chest tube output ≥2L within a 24-h period
- Type 5: fatal bleeding

  Type 5a

  Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious

  Type 5b

  Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

vii. Stroke with documentation on imaging (eg CT or MRI) of

- **Haemorrhagic**: a stroke haemorrhage in the cerebral parenchyma or a sub-dural or subarachnoid haemorrhage.
- **Ischaemic**: documented history of stroke or cerebro-vascular accident (CVA) resulting from an ischaemic event where the patient suffered a loss of neurological function with residual symptoms remaining for at least 24 hours.

15. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

a. Determination of sample size

In the existing CONCORDANCE data set (n=5396), 2320 (43%) patients are classified as high-risk (GRS greater than 118). Among these, the mean use of guideline recommendations (use of coronary angiography, discharge on at least 4 of aspirin, statin, $P2Y_{12}$ inhibition, beta-blocker, ACE-inhibitor/ARB, and referral to any secondary prevention program) is 49.7%. Assigning each of the three above indices of guideline adherence a score of one, (i.e. inpatient angiography=1, discharge on optimal medical therapy=1, rehabilitation referral=1) results in a proportion of optimally treated patients of 43%, with an ICC of 0.16.

To observe an increase in the proportion to 64% assuming and the intra-cluster correlation is 0.16 with >80% power and an alpha of 0.05 will require a sample size of 15 clusters per arm

with >37 individuals per cluster per arm. Therefore, this study will enroll 40 high-risk patients per cluster or 600 patients per arm. However, it will be important to recruit all patients presenting with an ACS diagnosis regardless of risk as their management will also likely be influenced by the intervention and the benefits of some recommendations (like angiography) are not as well established in this group. The total samples size will therefore be inflated 2.5 fold (100 patients per site to 3000 patients). Outcomes in this whole cohort will be assessed as a secondary endpoint.

Secondary endpoint (clinical events):

In the ACACIA study (conducted during 2006-7, 39 centres in Australia, many of whom have agreed to participate in CONCORDANCE for this study). In this study, 2704 patients were admitted with either STEMI or high-risk ACS and by discharge, 64 (2.5%) had died and 419 (15.9%) were not deemed to have an ACS diagnosis. Of those surviving to hospital discharge, 1053 (47.4%) died, suffered a recurrent MI, or required a cardiovascular readmission within 12 months. From our data, we estimated the ICC to be 0.031. To assess clustering of the composite clinical outcome measure by hospital, the intra-class correlation coefficient (ICC) was calculated from 3402 patients (39 centers throughout Australia).

By sampling 50 high-risk patients (GRACE score >118) from each of 15 hospitals in each group (30 hospitals in total), will achieve 82% power to detect a difference in the composite endpoint of 20% (48.0% in the usual care group vs. 38.4% in the intervention group) using a two-sided Z test (un-pooled), with a significance level of 0.050, and with the ICC set at 0.031.

This would require a total sample size of approximately 5800 in each group, beyond the capacity of the AGRIS study. To optimize the likelihood of detecting an effect on clinical outcome we plan a pre-specified meta-analysis combining data from this study and closely related Cluster RCTs being conducted in Canada, the United Kingdom and Asia.

b. Description of analysis sets

Primary analysis set

Primary Performance Measure Analysis: The primary analysis will compare the risk stratification using GRACE risk tool- and treatment recommendation plan versus standard therapy in improving the primary performance measure endpoint (application of all guideline recommended therapies at baseline). Given the heterogeneous population of patients who present with suspected ACS, combined with the difficulty in assessing application of guidelines among those patients who die in hospital, the primary analysis population will be confined to those patients discharged alive with an ACS diagnosis (STEMI, NSTEACS or unstable angina). Correlations between achievements of performance measures and late events will also use the primary analysis population.

Clinical Endpoint Analysis: The main analyses assessing the impact of risk stratification using GRACE risk tool on the primary clinical endpoint will be applied

to all patients who have not opted out of the study and have a GRACE risk score of >118 at the time of enrolment/admission.

Secondary analysis set

Secondary analyses of late clinical outcomes including cardiovascular mortality, recurrent MI, new or worsening heart failure and readmission for cardiovascular disease including bleeding events will use the entire study population who have not opted out of the study ie; entire intention-to-treat population.

Health economic analysis: quality-of-life, and cost-effectiveness analyses will be applied to all patients providing informed consent (for PBS and MBS data) at the time of enrolment.

c. Methods of statistical analyses

A flow chart showing the flow of patients through the trial and reasons for drop out or withdrawals will first be provided. The two groups will then be compared on baseline characteristics, with Chi-squared tests undertaken for categorical variables, and independent samples t-tests for continuous variables. Non-parametric analyses will be used where necessary. The primary analysis will compare the efficacy of risk stratification with GRACE- risk score intervention versus standard care in improving the primary performance measure endpoint in the population alive at the time of discharge and among patients with a GRACE score>118 for the primary clinical endpoint. To account for between-cluster variance, a GEE regression model with log link and binomial family will be used for this purpose. The initial analysis will simply compare composite outcome rates at 12 months between the two groups. Any variables in baseline analyses that differ between the two groups will then be included in the GEE model. The primary analysis will be on an intention to treat basis. Multiple imputations may be used to replace missing values if the assumptions appear to have been met.

Differences between the groups in freedom from mortality, recurrent MI and cardiac readmission (i.e. the individual components of the composite outcome)will be assessed by Cox proportional hazards model survival analysis. The relationship between clinical guideline adherence (as measured by performance indicators) and late clinical events among individual patients will also be evaluated in survival analysis.

Secondary outcomes including the interactions between the GRACE score use and hospital or clinical service characteristics, and ACS performance measures and late clinical outcomes will be examined using two-level random effects linear and logistic regression models respectively (STATA 12: xt commands). These models will include hospital level and patient level variables such as type of facility, number and qualification of medical staff, onsite invasive services, existing presence of clinical pathways etc. Given the small sample of hospitals included in this study, this component of the analysis will remain highly exploratory and will have limited power

to detect interactions between hospital characteristics and efficacy of decision support. Nevertheless, observations from this analysis will be used to inform future projects. All analyses will be undertaken using the STATA 12 statistical package.

d. Interim analyses

As there will be limited capacity to modify the study prior to completion, no formal interim analysis will be undertaken.

LIST OF REFERENCES

1. Huynh LT, Chew DPB, Sladek RM, Phillips PA, Brieger DB, Zeitz CJ. Unperceived treatment gaps in acute coronary syndromes. International Journal of Clinical Practice. 2009 Oct;63(10):1456–64.

2. Scott I, Derhy P, O'Kane D, Lindsay K, Atherton J, Jones M. Discordance between level of risk and intensity of evidence-based treatment in patients with acute coronary syndromes. Med J Aust. 2007 Aug 1;187(3):153–9.

3. Fox K, Anderson F, Dabbous O, Steg P, Lopez-Sendon J, de Werf Van F, et al. Intervention in acute coronary syndromes: do patients undergo intervention on the basis of their risk characteristics? The Global Registry of Acute Coronary Events (GRACE). Heart. 2007 Feb 1;93(2):177–82.

4. Hung J, Brieger DB, Amerena JV, Coverdale SG, Rankin JM, Astley CM, et al. Treatment disparities and effect on late mortality in patients with diabetes presenting with acute myocardial infarction: observations from the ACACIA registry. Med J Aust. 2009 Nov 16;191(10):539–43.

5. Joynt KE, Huynh L, Amerena JV, Brieger DB, Coverdale SG, Rankin JM, et al. Impact of acute and chronic risk factors on use of evidence-based treatments in patients in Australia with acute coronary syndromes. Heart (British Cardiac Society). 2009 Sep pp. 1442–8.

6. Majumdar S, Roe M, Peterson E, Chen A, Gibler W, Armstrong P. Better outcomes for patients treated at hospitals that participate in clinical trials. Arch Intern Med. 2008 Mar 1;168(6):657–62.

7. Astley CM, Macdougall CJ, Davidson PM, Chew DP. Lost in translation: health resource variability in the achievement of optimal performance and clinical outcome. Circulation: Cardiovascular Quality and Outcomes. 2011 Sep 1;4(5):512–20.

8. Granger C, Goldberg R, Dabbous O, Pieper K, Eagle K, Cannon C, et al. Predictors of hospital mortality in the global registry of acute coronary events. Arch Intern Med. 2003 Oct 1;163(19):2345–53.

9. Eagle KA, Lim MJ, Dabbous OH, Pieper KS, Goldberg RJ, de Werf Van F, et al. A validated prediction model for all forms of acute coronary syndrome: estimating the risk of 6-month postdischarge death in an international registry. JAMA. 2004 Jun 9;291(22):2727–33.

10. Fox KAA, Dabbous OH, Goldberg RJ, Pieper KS, Eagle KA, de Werf Van F, et al. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). BMJ. 2006 Nov 25;333(7578):1091.

11. Mehta SR, Granger CB, Boden WE, Steg PG, Bassand J-P, Faxon DP, et al. Early versus delayed invasive intervention in acute coronary syndromes. The New England journal of medicine. 2009 May pp. 2165–75.

12. 2011 Writing Group Members, Wright RS, Anderson JL, Adams CD, Bridges CR, Casey DE, et al. 2011 ACCF/AHA Focused Update of the Guidelines for the Management of Patients With Unstable Angina/ Non-ST-Elevation Myocardial Infarction (Updating the 2007 Guideline): A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2011 May 9;123(18):2022–60.

13. Chew DP, Aroney CN, Aylward PE, Kelly A-M, White HD, Tideman PA, et al. 2011 Addendum to the National Heart Foundation of Australia/Cardiac Society of Australia and New Zealand Guidelines for the management of acute coronary syndromes (ACS) 2006. Heart Lung Circ. 2011 Aug;20(8):487–502.

14. Authors/Task Force Members, Steg PG, James SK, Atar D, Badano LP, Lundqvist CB, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC). European Heart Journal. 2012 Aug 24.

15. Antman EM, Cohen M, Bernink PJ, McCabe CH, Horacek T, Papuchis G, et al. The TIMI risk score for unstable angina/non-ST elevation MI: A method for prognostication and therapeutic decision making. JAMA. 2000 Aug 16;284(7):835–42.

16. Morrow DA, Antman EM, Charlesworth A, Cairns R, Murphy SA, de Lemos JA, et al. TIMI risk score for ST-elevation myocardial infarction: A convenient, bedside, clinical score for risk assessment at presentation: An intravenous nPA for treatment of infarcting myocardium early II trial substudy. Circulation. 2000 Oct 24;102(17):2031–7.

17. Mehran R, Pocock SJ, Nikolsky E, Clayton T, Dangas GD, Kirtane AJ, et al. A risk score to predict bleeding in patients with acute coronary syndromes. Journal of the American College of Cardiology. 2010 Jun pp. 2556–66.

18. Subherwal S, Bach RG, Chen AY, Gage BF, Rao SV, Newby LK, et al. Baseline Risk of Major Bleeding in Non-ST-Segment-Elevation Myocardial Infarction: The CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines) Bleeding Score. Circulation. 2009 Apr 13;119(14):1873–82.

19. Chew DP, Huynh LT, Liew D, Astley C, Soman A, Brieger D. Potential survival gains in the treatment of myocardial infarction. Heart. 2009 Nov;95(22):1844–50.

20. Brieger D, Kelly A-M, Aroney C, Tideman P, Freedman SB, Chew D, et al. Acute coronary syndromes: consensus recommendations for translating knowledge into

action. The Medical journal of Australia. 2009. pp. 334–8.

21. Coiera E, Westbrook J. Should clinical software be regulated? Med J Aust. 2006 Jun 1;184(12):600–1.

22. Han Y, Carcillo J, Venkataraman S, Clark R, Watson R, Nguyen T, et al. Unexpected increased mortality after implementation of a commercially sold computerized physician order entry system. Pediatrics. 2005 Dec 1;116(6):1506–12.

23. Aliprandi-Costa B, Ranasinghe I, Turnbull F, Brown A, Kritharides L, Patel A, et al. The design and rationale of the Australian Cooperative National Registry of Acute Coronary care, Guideline Adherence and Clinical Events (CONCORDANCE). Heart Lung Circ. 2013 Jul;22(7):533–41.

24. Granger CB, Goldberg RJ, Dabbous O, Pieper KS, Eagle KA, Cannon CP, et al. Predictors of hospital mortality in the global registry of acute coronary events. Archives of Internal Medicine. 2003 Oct 27;163(19):2345–53.

25. de Araujo Goncalves P. TIMI, PURSUIT, and GRACE risk scores: sustained prognostic value and interaction with revascularization in NSTE-ACS. European Heart Journal. 2005 Mar 21;26(9):865–72.

26. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third universal definition of myocardial infarction. 2012. pp. 1581–98.

27. Kim J, Henderson RA, Pocock SJ, Clayton T, Sculpher MJ, Fox KAA, et al. Health-related quality of life after interventional or conservative strategy in patients with unstable angina or non-ST-segment elevation myocardial infarction: one-year results of the third Randomized Intervention Trial of unstable Angina (RITA-3). JAC. 2005 Jan 18;45(2):221–8.

28. Glasziou P, Simes R, Gelber R. Quality adjusted survival analysis. Stat Med. 1990 Nov 1;9(11):1259–76.

29. Rao SV, O'Grady K, Pieper KS, Granger CB, Newby LK, Mahaffey KW, et al. A Comparison of the Clinical Impact of Bleeding Measured by Two Different Classifications Among Patients With Acute Coronary Syndromes. J Am Coll Cardiol. 2006 Feb;47(4):809–16.

30. Stone G, McLaurin B, Cox D, Bertrand M, Lincoff A, Moses J, et al. Bivalirudin for patients with acute coronary syndromes. N Engl J Med. 2006 Nov 1;355(21):2203–16.

31. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. 2011. pp. 2736–47.

Intervention site

APPENDIX 1

Patient with ACS: positive ischaemic ECG/ troponin/ past history or new documentation of heart disease

Opt off consent to increase consecutive recruitment then study coordinator could approach patient during hospital admission for *opt in* consent to Medicare data

CLINICIAN DRIVEN BY DESIRE

TO DELIVER BEST PRACTICE CARE

- Leadership paramount from ED heads, ED senior MOs, cardiology heads, consultants on ward rounds etc
- Worksheet must add value in the clinical workflow

ED clinician:

4. Medical admission
5. Complete GRACE risk score and insert worksheet /sticker in the patient medical record and/or enter the score into the EMR
6. Refer to the decision-making pathway

Ward clinician:

1. Medical admission
2. Complete GRACE risk score and insert worksheet /sticker in the patient medical record and/or enter the score into the EMR
3. Refer to the decision-making pathway

STUDY COORDINATOR:

HREC Submission

Opt-out consent

EQ5D

Case record file

Source docs

Follow-up

EXTERNAL TRAINERS:

Site education regarding worksheet pivotal to be conducted by on-site by clinical leader (1x clinician and 1 x external trainer) with whole multidisciplinary team- nursing, medical, senior and junior, pharmacists, cardiac rehab during the regular site clinical meetings

External trainers would also have a monitoring role, regular site catch-ups over phone with PI etc to drive leadership

Drug Substance	
Study Number	ISSBRIL0166
Version Number	Version 7.0
Date	10th December 2015

A Cluster Randomised Trial of Objective Risk Assessment versus standard care for Acute Coronary Syndromes

Investigator Signature Page

1.1 Title of the Study: Australian Grace Risk Implementation study (AGRIS)

The Steering Committee approves the contents of this protocol and agrees the protocol contains the information required for the proper conduct of this study.

Steering Committee Chairs;

Name: Professor David Brieger	Sign:	Date:
Name Professor Derek Chew		

To indicate your agreement with the protocol, please sign and date below:

AGREED AND ACCEPTED
PRINCIPAL INVESTIGATOR
[Insert Name]
[Insert Date]

TABLE OF CONTENTS PAGE

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
ACACIA	Australian acute CoronAry Syndrome ProspeCtIve Audit
ACS	Acute Coronary Syndrome
ACUITY	Acute Catheterization and Urgent Intervention Triage Strategy
Angio	Coronary Angiogram
BBB	Bundle Branch Block
CABG	Coronary Artery Bypass Graft
CPK	Creatine phosphokinase
CPK-MB	Creatine phosphokinase-MB
CT	Computerized Tomography scan
DCF	Data Collection Form
DOB	Date of Birth
DM	Data Management
ECG	Electrocardiogram
EF	Ejection Fraction
GCP	Good Clinical Practice
GEP	Good Epidemiological Practices
GRACE	Global Registry of Acute Coronary Events
HB	Haemoglobin
ICH	International Conference of Harmonization
IRB/IEC	Institutional Review Board / Independent Ethics Committee
LBBB	Left Bundle Branch Block
MI	Myocardial Infarction
MRI	Magnetic Resonance
MR	Mitral Regurgitation
NSTEMI	Non-ST Elevation Myocardial Infarction
PCI	Percutaneous Coronary Intervention
SAP	Statistical Analysis Plan
STEMI	ST Elevation Myocardial Infarction
TIA	Transient Ischemic Attack
TIMI	Thrombolysis in Myocardial Infarction
VT	Ventricular Tachycardia

1. INTRODUCTION

Clinical risk stratification is the essential step in the effective and efficient translation of proven therapies into improved clinical practice. Yet, in acute coronary syndromes (ACS) care, we know that clinical risk assessment based on physician perception is heterogeneous. This study seeks to enhance evidence-based decision-making and outcomes by evaluating the impact of objective risk score-based decision-making using the GRACE risk tool together with recommendations for evidenced based care versus standard care in a hospital-level cluster-randomised implementation trial.

2. BACKGROUND

2.1 Potential opportunities for reducing morbidity and mortality in Australian ACS care.

Outcomes among the many patients presenting with ACS are compromised by the imperfect use of currently available therapies. Examples from the Australian clinical context observe that reperfusion for ST elevation myocardial infarction (STEMI) is provided in only 70% of eligible patients and complete prescription of guideline-advocated discharge therapies are provided in only 43% of patients.[1,2] Further contemporary evidence of this comes from the SNAPSHOT ACS study.

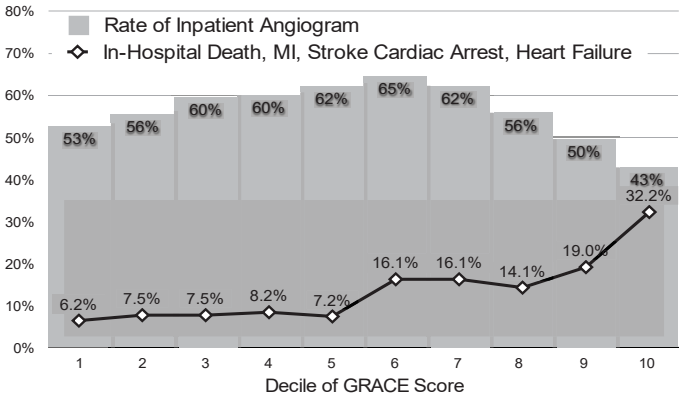

Figure1. High risk patients receive less invasive management.

Among the 2365 ACS patients enrolled from 286 participating hospitals within a 2-week period, a steep decline in the provision of early invasive management with increasing GRACE score in the upper deciles is still seen despite an increase in in-hospital death, recurrent myocardial infarction, stroke, cardiac arrest and new onset heart failure (Figure 1). Ample local and international evidence demonstrates poorer long-term outcomes among patients not receiving evidence-based therapies. Closing this evidence gap represents a near-term goal in health agendas around the world. *The key translational challenge resides in defining those interventions that may bridge this evidence practice gap in an effective and cost-effective manner.*

2.2 Clinical Risk Stratification: A translation gap

2.2.1 Limited objectivity in the provision of care: Previous studies have illustrated a disconnect between physician-perceived use of guideline-based therapies and their actual use by surveying physicians at each hospital upon completion of a site-specific audit in the ACACIA study.(1) Overall, correlation between perceived and actual use for guideline therapies was very poor (highest correlation $r=0.31$ ($p<0.01$) for use of invasive management)

with perceived grossly overestimating actual use (Figure 2). In contrast, when clinical guideline content was assessed, clinicians scored highly (~70%), underlining that *difficulties in translating knowledge, rather than the lack of knowledge per se, may explain this disconnect*.

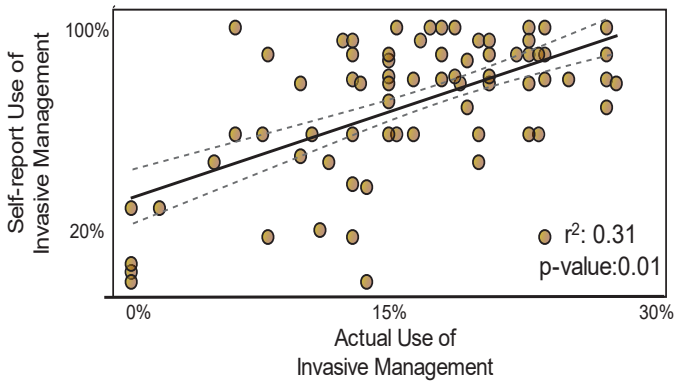

Figure 2: Correlation between observed and physician estimated rates of invasive management use in ACS patients.

2.2.2.Patient complexity: Several analyses have observed lower rates of evidence-based therapy use among higher risk groups.(2-4) Dissecting this relationship further, a strong relationship between the use of evidence-based therapies and increased myocardial risk (either ECG or biomarker abnormalities or haemodynamic compromise), but a strong negative correlation between guideline use and the presence of co-morbid medical conditions, such as renal impairment, chronic lung disease, prior heart failure, cerebrovascular disease and advanced age has also been demonstrated.(5) Integrating evidence into patient complexity is challenging. When patients "fit the evidence" guideline care is more frequently applied, but when they do not, uncertainty in applying the evidence persists. It is sobering to recognize that ~2% of patients contribute to the clinical trial evidence base, while clinical trials often actively exclude patients with significant co-morbidities.(6) *A greater capacity for risk stratification and support in weighing of risk and benefit may assist both cardiovascular and non-cardiovascular specialists to extend the current evidence-base to greater proportion of patients and potentially further improve outcomes.*

2.2.3. Misperceptions of patient risk impacts practice and outcome.
A study of physician perception of risk compared with objective risk stratification provided by the GRACE risk score among 1542 ACS patients in Australia, China, India and Russia has recently been completed. For each specific patient, 2 or 3 physicians (81% with a cardiovascular specialist qualification, median time from medical qualification: 10 years) directly involved in the patients care were asked to assess the patients "untreated" risk of death by 6 months and then determine the value of the impact of current guideline recommended therapies. (PREDICT study: Accepted Circ. CV Outcomes and Quality 2013) Compared with the GRACE risk score, physicians generally over-estimated low risk patients and under-estimated high risk patients. Consequently, the GRACE risk score was superior to physician estimation of 6-month mortality (C-statistic: GRACE score: 0.81 versus Physician Estimation: 0.65, P<0.001).

Adding the GRACE score to physician estimation increased risk discrimination (Integrated Discrimination Index (S.E.): 0.063 (0.012), p<0.001). Furthermore, when care was correlated with physician perception of risk, percutaneous coronary intervention (PCI) rates were higher among those at increased risk (Figure 3). In contrast, when care was correlated with objectively measured risk using the GRACE risk score, lower PCI rates among high-risk patients was evident. By 6-months, mortality rates were higher among patients in whom the risk was underestimated. (Not under-estimated: 10/967 (1.0%) vs. one physician underestimated: 25/429 (5.8%) vs. all physician's underestimated: 13/146 (8.9%). After adjusting for GRACE risk and frailty, any physician underestimation of risk was associated with a 6.0 fold increase in 6-month mortality (95% C.I.: 2.3-15.5, p<0.001). (PREDICT study: Personal Communication). It is intuitive that improving physician application of risk stratification will improve outcomes, however this hypothesis, which is derived from these observational data, needs to be prospectively tested.

2.2.4 Contextual factors that facilitate care: Hospital level processes for implementing guidelines such as protocols, knowledge resources and workforce characteristics have often evolved without evaluation of their impact on outcomes. The specific system-based decision tools such as the formal implementation of objective risk stratification designed to facilitate guideline application and better outcomes warrant closer exploration. Evaluation of the system-based components of ACS care among 35 Australian hospitals has observed heterogeneity in the implementation of quality improvement tools with poor correlation between these strategies and outcomes.(7)However, those patients treated in a hospital with an electronic process for ensuring evidence-based application experienced a 51% reduction (Odds ratio 0.49, C.I. 95% CI; 0.35-0.68, p <0.001) in 12-month mortality.(7)*Active design of clinical processes conducive to the delivery of evidence-based care may represent an opportunity to improve clinical outcomes.*

2.3 Objective risk assessment in ACS: the GRACE risk score

The GRACE risk score is a set of clinical risk stratification indices developed from >100,000 patients enrolled from 247 hospitals in 30 countries.(8,9) Using age, haemodynamics, ECG changes, cardiac marker elevation and renal function, this objective assessment of risk has been validated in several dataset including several Australian cohorts including ACACIA,CONCORDANCE and PREDICT, C-statistic 0.81).(10) In a recent study, the admission GRACE risk score identified those patients who benefitted from early angiography and revascularization (<48 hours). (11) Importantly however, the prospective routine application of a risk score into clinical decision making has not been shown to result in improved outcomes in the broader cohort of ACS patients. Despite this, its routine use has been advocated in the current American and European as well the

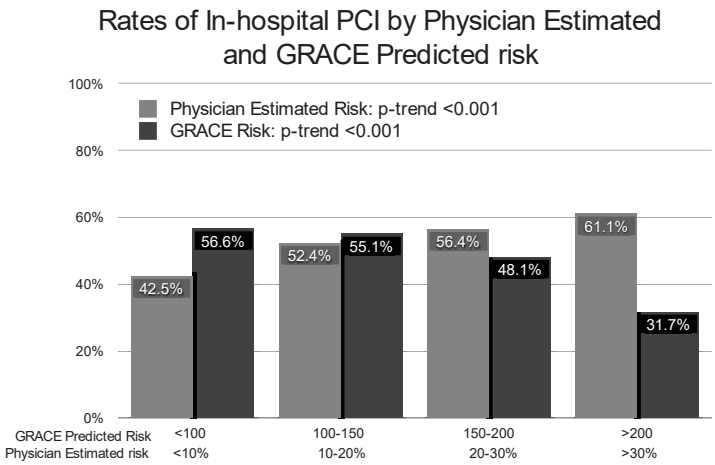

Figure 3. Rates of in-hospital PCI by Physician estimated and GRACE predicted risk

Australian and New Zealand ACS guidelines (e. Class IB indication in ESC Guidelines for management of NSTEACS). (11-14) The use of the risk tool at the bedside is limited, in part due to poor awareness of how it may influence clinical decision-making and, a strong reliance on doctor estimated risk. *Clinical equipoise regarding the utility of the GRACE risk score in ACS management remains, and the limited utilization provides an opportunity to evaluate the impact of routine application on clinical practice and outcomes.*
Other risk scores: Other risk scores for the prediction of ischaemic and bleeding risk have also been developed. These include the Thrombolysis in Myocardial Infarction (TIMI) risk scores for ST elevation MI (STEMI) and non-ST elevation ACS (NSTEACS), as well as the ACUITY and CRUSADE risk scores for the prediction of major bleeding events.(15-18) For ischaemic events, the TIMI risk scores, which have been derived from clinical trial populations, are also superior to clinical perception but appear inferior to the GRACE risk score. However, the prediction of bleeding events by the ACUITY and CRUSADE scores is poor as is physician perception. (PREDICT study: Accepted Circ. CV Outcomes and Quality 2013).

2.4 Translation Research: From National Agenda to Local Practice
2.4.1 The optimal application of current ACS evidence-based care is expected to provide greater survival gains than further innovation in any specific therapy. In an analysis drawn from contemporary Australian ACS practice and randomised clinical trial (RCT evidence), an system-wide approach aiming to provide a 25% increase in guideline adherence to the entire population has the potential to save 82 lives per 10,000 presentations with direct cost saving of > $300 million to the Australian community per year.(19) In contrast, since relatively few patients receive complete care, a novel therapy providing the same 25% mortality reduction among those already receiving all guideline recommendations would save only 5 lives saved per 10,000 presentations.(19) *These observations define the need for strategies that improve decision making to drive evidence to outcome for all ACS patients.*(20)

3. RESEARCH HYPOTHESIS

Objective risk stratification using the GRACE Risk Tool and treatment recommendation plan improves the achievement of hospital-level performance measures, and secondarily, provides a cost-effective approach to improving ACS outcomes.

Rationale for conducting this study
The interaction between health care provider and patient remains at the core of efforts to translate evidence to outcome. In part, modern sophisticated ACS care has relied on expert clinical intuition together with responsive integrated health care delivery for the timely provision of optimal care. ***Refining risk-based decision-making to reduce access inequities in rural, outer metropolitan communities due to limited expert care, while informing "misperceptions" of risk that lead to under-treatment of high-risk patients in metropolitan hospitals are the essential objectives of this proposal.*** Such innovations would also have significant relevance in countries where access to expert care is hampered by geographic distance such as Australia, or where the workforce capacity is challenged by the burden of care resulting from the urbanization of developing economies.

Contemporary data indicate under-utilization of early invasive management and proven pharmaco-therapies in ACS care. Approximately 1 in 2-3 patients will die, suffer recurrent MI or require readmission by 1 year after admission for MI. Effective ACS management requires rapid and accurate risk assessment and the timely delivery of resource intensive therapies. Faced with increasing patient complexity, where relative risks and benefits are often more difficult to weigh, it is not surprising that current care remains sub-optimal. An intervention providing contextual evidence-based decision-support support directly at the point of care may be a step forward in improving clinical outcomes by improving clinical guideline adherence and reducing inequities in health care provision through the support of clinical capacity in rural areas. However, the validity of this strategy is unproven and should be tested within a robust randomized comparison. Understanding the relative impact of this approach will inform current efforts to minimize the heterogeneity in ACS care through the use of evidence-based decision support, not only in ACS care but also across the broader emerging Health agenda.

a. Benefit/risk and ethical assessment

This study is assessing a practice-level intervention directed at acute hospital care. Current evidence suggests that under-appreciation of risk is prevalent and is associated with reduced access to care and worse clinical outcomes. The anticipated benefit to patients cared for in hospitals randomised to risk stratification using the GRACE risk tool and treatment recommendation plan, is that the new protocol may be associated with improved adherence to evidence-based care and clinical outcomes. However, there remains a risk that patients cared for in hospitals randomised to the risk stratification tool and treatment recommendation plan will have an increased incidence of procedure or drug related complications without an improvement in outcomes. Consistent with this, one study has shown that electronic decision support in the intensive care environment has been associated with an increase in morbidity and mortality.(21, 22) Hence, equipoise regarding the study question remains. This study will employ a Data Safety Monitoring Committee to monitor the progress of the study.

4. STUDY OBJECTIVES

This study seeks to enhance evidence-based decision-making and objective delivery of acute coronary syndromes (ACS) care by evaluating the benefit of risk stratifying ACS patients using the GRACE Risk tool and treatment recommendation plan versus standard care in a hospital-level cluster-randomised clinical trial design.

a. Primary objective

Evaluate the effectiveness of risk stratification using the GRACE Risk tool and treatment recommendation plan for ACS patients on the in-hospital use of evidence-base investigations and therapies and secondary prevention assessed at the time of discharge.

b. Secondary objectives

1. Determine the incremental net clinical benefit and cost-effectiveness of risk stratification using the GRACE Risk tool and treatment recommendation plan on care within the routine clinical environment;
2. Determine the incremental net clinical benefit of risk stratification using the GRACE Risk tool and treatment recommendation plan on the reduction of cardiovascular death, myocardial infarction, new or worsening heart failure, and cardiovascular readmissions at 12 months.

This study will be conducted as part of an international network of cluster-randomised studies evaluating risk stratification using the GRACE Risk tool and treatment recommendation plan within the United Kingdom, Canada, and the Asian region, and will contribute to a planned meta-analysis of these studies evaluating the impact on death or recurrent myocardial infarction.

c. Exploratory objectives

1. To correlate clinical performance measured by established performance indicators in ACS with 12-month clinical outcomes;
2. To explore the health service characteristics associated with higher and lower performance on ACS clinical performance indicators and the interaction with risk stratification using the GRACE Risk tool and treatment recommendation plan.

5. STUDY PLAN AND PROCEDURES

a. Overall study design and flow chart

To evaluate the effectiveness of objective risk stratification using the GRACE Risk tool and treatment recommendation plan versus standard care for improving the use of evidence-based investigations, therapies and secondary prevention in hospital. A cluster-randomised implementation trial with blinded endpoint evaluation for clinical events recorded in-hospital and during the follow-up period will be used. (Figure 4: Cluster randomized design of GRACE risk score versus standard care study schematic).

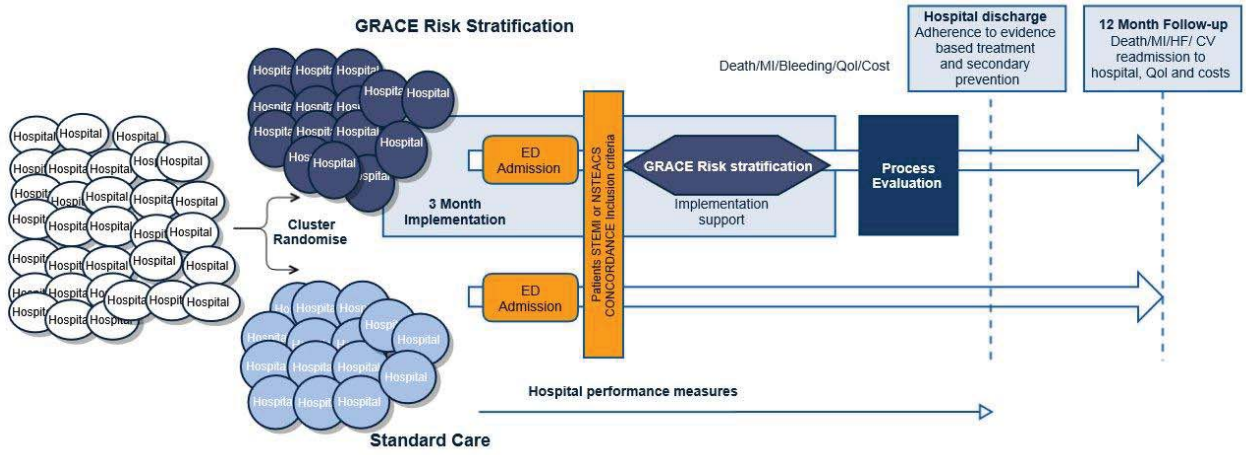

Figure 4: Cluster randomised design of GRACE risk score versus standard care

b. Rationale for study design

Given that clinical care among patients within hospitals is correlated and the intervention is system-based, randomisation and the implementation of the GRACE Risk tool and treatment recommendation plan will be required to prevent between clinician contamination. Since the system-level intervention directed at supporting decision-making is under investigation, blinding of the intervention is not appropriate. Hence, this study will employ a prospective randomised open-label blinded endpoint (PROBE) design and employ a blinded event adjudication committee, relying on objective measures of hospital performance and clinical events. Furthermore, to avoid selection bias occurring within each hospital site, consecutive enrollment of all eligible patients admitted to the site within the enrolment period will be sought using an "opt-out consent" process.

6. HOSPITAL AND PATIENT SELECTION CRITERIA

a. Hospital-level Inclusion criteria

Public Hospitals from metropolitan and regional/rural centres that fulfill the following characteristics will be eligible to participate:

- The presence of an onsite 24/7 emergency service.
- ED, Cardiology/medicine services willing to implement the GRACE Risk tool and treatment recommendation plan into their care process.

Hospitals will be stratified by size of hospital and hospital performance in key process measures. (23) Randomisation will reflect equal representation of hospitals across each stratified tier in both arms of the study.

Hospitals with an existing implemented risk stratification support system for the management of ACS patients will be excluded.

b. Patient-level Inclusion criteria

Patients are eligible if they present to hospital with symptoms felt to be consistent with acute cardiac ischaemia for >10mins within 24 hours of presentation to hospital **plus** one of the following: ECG changes; elevated enzymes; documentation of CAD or documentation of 2 or more features of high risk ACS.

ECG changes:

- transient ST segment elevation of 0.5mm in two or more contiguous leads;
- ST segment depression of 0.5mm in two or more contiguous leads
- new T wave inversion of 1 mm in two or more contiguous leads
- new Q waves (1/3 height of R wave or >0.04 seconds)
- new R wave > S wave in lead V1 (posterior MI)
- new left bundle branch block

Increase in cardiac enzymes:

- increase in troponin T above the upper limit of normal;
- increase in troponin I above the upper limit of normal;
- CK-MB 2x upper limit of the hospitals normal range **or** if there is no CK-MB available, then total CK greater than the upper limit of normal.

Documentation of Coronary Artery Disease:

- history of MI, angina, congestive cardiac failure due to ischaemia or resuscitated sudden cardiac death;
- history of, or new positive stress test with or without imaging;
- prior or new, cardiac catheterisation documenting coronary artery disease;

- prior, or new percutaneous coronary artery intervention or coronary artery bypass graft surgery.

At least 2 of the following High Risk features:

- haemodynamic compromise (BP<90 and HR >100)
- left ventricular systolic dysfunction (LVEF<0.40);
- presence of known diabetes
- documentation of chronic kidney disease (estimated GFR <60mls/min)

Permission to include ACS patients who meet the above inclusion criteria but die before the opt-out consent process will be included using a waiver of the opt-out process. Approval will be sought from each local Human Research Ethics Committee

Exclusion criteria

Patients presenting to hospital with an ACS accompanied with, or precipitate by significant co-morbidity e.g. motor vehicle accident, trauma, severe gastrointestinal bleeding, peri-operative or peri-procedural MI will be excluded. Patients already recruited into the study cannot be re-enrolled into the study.

7. HOSPITAL RANDOMISATION AND SUBJECT ENROLLMENT

a. Procedures for Hospital randomisation to the GRACE Risk tool and treatment plan

Cluster randomisation will be undertaken at the level of the hospital (1:1, GRACE Risk tool and treatment recommendation plan versus usual care). An independent statistician will use a table of random numbers to assign half the hospitals to the intervention ensuring that hospitals across each stratified tier will be represented in both arms of the study. The concealed randomised allocation will be revealed to the hospital only after all ethical and research governance documentation has been completed and the site is ready to initiate the study.

b. The GRACE Risk tool and treatment plan

1. **Risk stratification using the GRACE risk tool and treatment recommendation plan.** The GRACE risk tool and treatment recommendation plan is a patient-level clinical risk stratification worksheet with simple treatment recommendations applied within those hospitals randomised to the active arm. The tool will be implemented through either a paper-based worksheet or electronic medical records within the hospital at the earliest time-point of the patient's admission to hospital. After assessment of basic clinical data including symptoms, clinical findings, past-history, ECG changes, biomarker elevation and basic biochemistry, the calculation of the GRACE Risk tool to predict in-hospital and 6-month mortality risk in all patients will be required.(9,10,24) Simple dichotomous management recommendations with respect to use and timing of early angiography and possible revascularization as well as anti-thrombotic therapies consistent with the NICE guidance, secondary prevention therapies and referral to cardiac rehabilitation will be made.(11,25)

Data, including all baseline measures and clinical assessments, therapies and timing of treatments, will be recorded in the electronic CONCORDANCE Registry case report form.

The worksheet will consist of the following risk stratification calculators, nomograms and clinical orders:

i. Ischaemic risk:

The ischaemic risk calculator will list key clinical information required to generate the latest version of the GRACE risk score available, and will provide the clinician with a numeric risk estimate for death and the composite of death or new/recurrent MI by 6-months.

ii. Bleeding risk:

An estimate of bleeding risk will also be provided using an internationally accepted bleeding risk scale.

iii. Nomograms:

Nomograms for the quantification of risk and benefits: will provide patient-specific incremental reductions in recurrent events using literature-based estimates of treatment effect associated with invasive management and secondary prevention therapies. A nomogram detailing the expected patient-specific risk of major bleeding events combined with recommendations associated with radial angiography, and use of antithrombotic therapy will also be provided. These will assist clinicians in deciding on the use of invasive management and facilitate communications with patients and families by providing the individualized expected absolute risk and expected benefits associated with specific guideline recommended

iv. Treatment recommendation plan:

Specific recommendations based on threshold values of the GRACE risks score or guideline recommended care will also be provided. A sample of the implementation tool is included (see Appendix…) In order to maximise uptake it will be permissible for sites randomised to the GRACE risk tool and implementation plan to modify both the layout of the tool, and the specific recommendations for inclusion in the tool to reflect local practice. Local changes will be approved by the Steering Committee who will ensure that these recommendations include the process measures that comprise the primary endpoint of the AGRIS study (ie coronary angiography, secondary prevention drugs and rehabilitation for high risk patients).

vi. Clinical orders:

The worksheet will include a section to enable the admitting clinician to document the intended therapies including prescription of acute and long-term guideline recommended therapies, specifying the need for and planned timing of invasive management, and referral to secondary prevention services. The ability to record whether each of these therapies is "indicated," "not-indicated" and "contra-indicated will also be included on the worksheet.

Where possible, it will be deployed at each hospital at the earliest time-point following admission to hospital. This worksheet will also serve as the source document for part of the case-report form for each participant of the study,

2) Standard care: Hospitals randomised to standard care will continue to approach and enroll consecutive ACS patients into the CONCORDANCE Registry using the opt-out consent process. Data, including all baseline measures and clinical assessments, therapies and timing of treatments, will be recorded in the electronic CONCORDANCE Registry case report form.

c. Implementation of the GRACE risk tool

The GRACE risk tool treatment recommendation plan will be embedded within the routine clinical assessment and management procedures at each of the hospitals randomised to the active arm. A 3-month implementation period will be followed by the active recruitment period (estimated 9-12 months).

Integration of the Grace Risk tool into the clinical workflow will require significant clinical leadership from local medical and nursing champions. Study resourced implementation experts will assist with this process. The engagement of local leaders will be necessary to a) appropriately influence and modify the admission documentation and clinical processes including identifying which specific local staff member is responsible for completion of the form (i.e. cardiac resident, or nursing) and b) facilitate communication regarding the relevance and utility of objective risk stratification to each component of the ACS team facilitating adherence to the new processes.

During the implementation period, an external trainer will work closely with the study site (i.e. local clinical lead, medical, nursing and allied health staff) to facilitate the incorporation of the risk assessment worksheet into current work practices, including the use of paper documentation, other risk calculators, and treatment protocols. The time and resources required in implementation will be included in the cost-effectiveness analysis.

The roles at of the external trainer and the implementation team at each hospital is separate to that of the clinical trial coordinator whose responsibilities are for the operational and regulatory aspects of the study including obtaining ethical and governance approval for the conduction of the study patient recruitment, management of the Grace Risk tool worksheet, data entry in the electronic CRF and reporting of clinical events.

Differentiation between the Grace Risk tool and treatment recommendation plan and usual care will be critical to the scientific integrity of this study. As a consequence, efforts will be made to ensure the consistent uptake of the intervention at the hospitals randomised to the active arm. Facilitating the completion and clinical influence of the GRACE risk tool may require several levels of engagement. While the specific characteristics of the implementation will vary between hospitals, the following principles will apply:

- Adjustment of the admission process to include risk stratification with the GRACE risk tool

- Communication on the clinical utility and relevance of the GRACE risk tool to the entire multi-disciplinary team, specific to their roles.

Calculation and documentation of the GRACE risk score will be completed by the medical officer completing the patient's admission or the senior clinical nurse depending on local circumstances and will be reviewed by a more senior medical clinician (i.e. medical registrar, cardiology registrar, consultant) where possible.

Efforts to extend the relevance of the GRS intervention to other disciplines within the acute care team (including nursing, pharmacy and cardiac rehabilitation) recognises significant variation in the levels of engagement, autonomy and authority to initiate care across hospitals. Consequently, a single standardised information session informing these disciplines of the potential value of the GRS intervention to their workflow will be undertaken early during the implementation phase.

d. Documentation of the GRACE Risk Score

The GRACE Risk tool will be provided to sites in paper form or incorporated into the electronic medical records if required and will be copied and collected as a source document to assess how it is applied in the clinical environment. The original form will remain in the patient medical record and uploaded into the patient care system where possible.

8. COLLECTION OF STUDY VARIABLES

a. Recording of data

Clinical data will be recorded on a web-based clinical record file (CRF) developed for the CONCORDANCE Registry.

b. Data collection at enrolment and follow-up

The GRACE Risk tool and treatment recommendation plan will be developed by a committee of experts in the treatment of patients with ACS and the systems and processes of care that apply in accordance with best practice evidence from clinical trials and guidelines where they exist.

Baseline Data

Baseline data will include demographic factors, cardiac risk factors, frailty index, current and past medical diagnoses and their timing, time to presentation, clinical risk stratification

parameters and clinical parameters reflecting processes of care as documented in the electronic and paper based medical record.

A more detailed survey for hospital and local barriers to implementation will be evaluated in a qualitative manner. These data will include;

- Geographical location, and whether rural or metropolitan
- Hospital type (academic/teaching; public; private)
- Total number of hospital beds
- What size population the hospital serves
- Number of ACS admissions per year
- Hospital facilities (Coronary Care Unit; Open Heart Surgery Theatre; number of cardiologists; number of interventional cardiologists; number of catheterisation laboratories, number of cardiac surgeons).
- Number of Coronary Angiograms performed per year
- Number of Primary PCI performed per year
- If the enrolling hospital does not have an onsite cath Lab, the name of the hospital where patients are referred to for interventional procedures
- Distance from enrolment hospital to hospital with interventional cath-lab facilities
- Presence of quality improvement staff

Follow-up procedures

Participants will be followed up at 12 months from the date of hospital discharge. Follow up visits may be performed via telephone, patient letter, General Practitioner contact, next of kin contact and/or hospital admission data base. If no participant data is available at the 12-month time point, the participant's name will be checked against the National Death Index for mortality status to ensure that all participants have an outcome listed at 12 months. If vital status is unable to be confirmed via the above methods including National Death Index or any other administrative registry if available, patients will be removed from the final analysis.

Late clinical evaluations (hospital discharge to final study visit) will be conducted by study coordinators and supplemented by hospital records and the National Death Index. Quality of life measures, using the 5-level EQ5D instrument, will also occur at 1 year.

c. Enrolment procedures and the opt-out consent process

The physician or study coordinator will check if the patient fulfils the inclusion and exclusion criteria. Hospital admission records will be used to generate screening logs to assist in the identification of eligible patients. Since this is a hospital level intervention and in order to avoid biased sampling of the ACS population patients are enrolled via an opt-out consent process.

Patients will receive an information sheet in lay-man's language. The patient, their relative or carer will be provided with the opt-out consent form detailing; why their data is being collected and how it will be used; what data will be collected ie; their identity and some clinical information; how their data may be linked and shared; details on how to opt-out of the study and the name and the phone number of the person to notify and the contact details of the hospital. Assurances will be made that they are able to opt-out at a later date and that the decision not to participate in the study will not affect their medical treatment or their relationship with the staff that are caring for them. They will also be given details on how to lodge a complaint through an independent complaints process.

In order to ensure the study is representative of all ACS patients, it is important to include the sub-set of patients who die early during their admission to hospital. Consent waivers will be sought for patients who die during their admission or are too ill to provide consent. This waiver ensures that sites are able to enroll consecutively and truly reflect the ACS population presenting to hospital. The approval for this will be determined by each site's governing ethics committee. For patients who lack the competence to provide consent, or where the patient is from a Non-English speaking background and has limited command of English hospital staff will approach a person with lawful authority on behalf of that patient (this is usually the next of kin or carer) with the opt-out information sheet for the study.

The opt-out consent process meets the guidelines for the collection of identifiable information as outlined within Australian Commission on Safety and Quality in Health Care (ACSQHC) report on development of operating standards for Australian Clinical Quality Registries (NEHTA) and the National Statement on Ethical Conduct in Human Research [1] [2] and Guidelines approved under Sections 95 and 95A of the Privacy Act 1988.

Patients are free to withdraw from this study at any time point during the course of the study. Upon withdrawal, the patient's data collected to that point will be included in the primary analyses unless the patient stipulates otherwise. No additional follow-up will be conducted.

d. Consent for data linkage to the Medicare and Pharmaceutical Benefits Schedules

In a subset of patients the physician/study coordinator will also obtain signed patient consent to access data from the Pharmaceutical Benefits Scheme (PBS) and Medicare Benefits Scheme (MBS). Patients will be informed how their data may be linked and shared and the type of data that will be collected. Theis data will contribute to the cost-effectiveness analysis.

e. Effectiveness

Clinical events will be identified through patient contact, and electronic and manual searches of hospital records, general practice notes and the National Death Index where possible. Where suspected events have been identified, source documents (described below) will be required to enable centralised clinical event adjudication.

f. Primary Outcome: Composite of ACS performance measures by hospital discharge:

The primary (hospital performance measure) endpoint will be the composite endpoint of adherence to the following performance measures by the time of discharge among those patients discharged alive:

i. Receipt of invasive or CT inpatient angiography during the index hospitalization where the patients GRS is >118.
ii. Prescription of at least 4 of the 5 clinical guideline advocated therapies drug classes at discharge if there is no stated contraindicated (patients with a stated contraindication will be coded as compliant). Specifically:
    (a) Aspirin≥100mg/day;
    (b) A beta-blocker;
    (c) A $P2Y_{12}$ inhibitor;
    (d) An ACE-Inhibition or ARB at discharge where is a history of hypertension, diabetes or known LV impairment (EF documented to be <50% by any form of cardiac imaging);
    (e) A HMG-CoA reductase inhibitor;
iii. Documentation of referral to cardiac rehabilitation services

Each of the criteria will be evaluated separately and aggregated to a possible score of 3 (i.e. 1 for inpatient angiography, 1 for at least 4 of the 5 secondary prevention pharmacotherapies, and 1 for referral to a secondary prevention program).

g. Secondary outcomes: Composite endpoint of cardiovascular death, new or recurrent myocardial infarction, new or worsening heart failure or cardiovascular readmission at 12 months

1. The secondary outcome is a clinical endpoint evaluated as the composite endpoint of cardiovascular death, new or recurrent myocardial infarction, in-hospital heart failure or cardiovascular readmission at 12 months defined as:

i. cardiovascular mortality
ii. New or recurrent MI defined as chest pain/discomfort associated with a rise and fall in cardiac biomarkers, or a new myocardial defect on echocardiography, and consistent with the new Universal Definition.(26)
iii. Development of new or worsening heart failure in hospital as evidenced by a deterioration in the Killip Class.
iv. Hospital admission for: unplanned coronary revascularization (non-elective PCI or CABG); cerebrovascular accidents with cerebral imaging; cardiac arrhythmias; CCF without MI; or unstable angina.

2. Cost-effectiveness evaluation

i. Health-related quality of life and associated utility estimated with the Assessment of Quality of Life (EQ5D) instrument at 1 year.(27)
ii. Resource use and cost over 12 months, including Medicare data in consenting patients (GP contact using Medical Benefits Schedule (MBS), medication use from Pharmaceutical Benefits Schedule (PBS) and in-patient admissions from the AN-Diagnosis Related Group (DRG) in participating hospitals.

The Investigator at each site is responsible for ensuring all local regulatory requirements and obligations relating to safety reporting to the Therapeutic Goods Administration following a serious adverse event that occurred following administration of a therapeutic drug during the study.

h. Patient reported outcomes (PRO)

Quality of life measures using the 5-level Euro-QoL 5D (EQ-5D) instruments, adherence to medical therapies, readmission to hospital with heart disease, planned and unplanned cardiovascular procedures, new or worsening heart failure and survival status will be collected via patient self -report 1 year. The EQ-5D is a standardised measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of health care as well as in population health surveys. EQ-5D is suited for use in postal surveys, in clinics, and in face-to-face interviews. It is cognitively undemanding, taking only a few minutes to complete.

i. Health economics

Patient level measures of utility derived from the EQ5D instrument will be integrated with survival curves to estimate quality adjusted life years in each trial arm using the quality-adjusted survival analysis (QASA) method.(28) Within-trial incremental costs associated with the GRACE risk tool and treatment recommendation plan and with standard care will be estimated from patient data on MBS, PBS and hospital use. Within-trial cost-effectiveness will then be analysed allowing for bivariate uncertainty with bootstrapping of patient costs and effects to maintain covariance structure. This analysis will include cost-effectiveness, acceptability, net benefit and expected net loss curves to inform decision makers of the optimal strategy at any given threshold, uncertainty around this decision and the potential value of further research locally and internationally.

j. Process evaluation

Semi-structured interviews with health care providers will be conducted in hospitals whose ability to implement the GRACE Risk tool and treatment recommendation plan is variable. Participants will include health care providers participating in the implementation process. A number of patient/hospital/system-level factors impact on a hospital's performance and identification of these factors and the degree to which they operate in each hospital is central to understanding why some patients receive care which is not in line with current management guidelines.

9. ETHICAL AND REGULATORY REQUIREMENTS

a. Ethics and regulatory review

Approval will be sought from each participating centre's Human Research Ethics Committee (HREC) and/or Governance Officer as required. Participation of medical practitioners, hospitals and patients in the study will be voluntary and approval from the local department and hospital executive will be required.

This study will be registered with Australian and New Zealand Clinical Trial Registry (www.anzctr.org.au).

b. The PBS and MBS Consent Process

Enrolment into the study will be via an opt-out consent process for main study. All patients will be informed of their right to withdraw from the study at any time without prejudice to their medical and/or nursing care at that time or in the future. Approval for to include and access the medical records of patients who meet the inclusion criteria but die before the opt-out information sheet is provided will be sought from the local hospital ethics committees.

Where possible, a subset of patients will be approached during their hospital admission and asked to sign the consent forms for access to data via the PBS and MBS in addition to linkage with the national hospital morbidity and mortality dataset. In order to ensure there is no impact on consecutive recruitment into the AGRIS study, patients may be consented for PBS, MBS and data linkage after recruitment into the study, that is at a later stage during their admission.

c. Data quality audits

The participating physician agrees to allow the /coordinating centre auditors to have direct access to his/her study records for review. It is understood that these personnel are bound by professional secrecy, and as such will not disclose any personal identity or personal medical information.The participating physician will make every effort to help with the performance of the data quality audits and inspections, giving access to all necessary facilities, data, and documents.

The confidentiality of the data verified and the protection of the patients will be respected during these inspections. Any result and information arising from the inspections by the competent authorities will be immediately communicated by the participating physician to the Sponsor and Coordinating centre. The participating physician shall take appropriate measures required by the coordinating centre to take corrective actions for all problems found during the audit or inspections.

Appropriate measures will be taken to ensure the security of personal data (including storage of paper records in locked cupboards/filing cabinets, restricted access to computer databases and separation of personal identifying data from the participant records). All assessment data sheets and files will contain subject ID only. The study database will be retained indefinitely

at Centre for Outcomes Research (COR) at The University of Massachusetts Medical School, Worster.

10. STUDY ORGANISATION

The study will be conducted by the Sydney Local Health district Concord Hospital and the Steering Committee is co-chaired by the PIs Professor David Brieger and Professor Derek Chew and includes the CIs and the Project Manager (PM). The Steering Committee has representation by senior cardiologists clinicians and statisticians from SLHD, Sydney University, the Cardiovascular Division of The George Institute for Global Health Sydney, the South Australian Health and Medical Research Institute (SAHMRI) and the University of Adelaide, SA. The Steering Committee is responsible for all aspects of the study design and implementation. It approves the final protocol, supervises enrolment and responds to the study management group, the data safety and monitoring board and clinical event adjudication committee. Analysis and manuscripts will be the responsibility of the Co-Chairs, CI's and PM. The PM and PI will produce half yearly and final reports.

The Steering Committee members include:

- Professor Derek Chew Co-Chair (Flinders University and Flinders Research Group Adelaide, South Australia)
- Professor David Brieger Co-Chair (Concord Hospital SLHD and Sydney University)
- Professor Anushka Patel (Chief scientific officer, The George Institute for International Health)
- A/Prof Graham Hillis (Co-Director Cardiovascular Division of The George Institute for International Health, Sydney)
- A/Prof Clara Chow (Cardiovascular Division of The George Institute for International Health, Sydney)
- Professor Laurent Billot (Senior Statistician at The George Institute for International Health, Sydney)
- Ms Bernadette Aliprandi-Costa (Senior Project Manager Concord Hospital SLHD and Sydney University)
- Dr Carolyn Astley (Flinders Research Group Adelaide, South Australia)
- Dr Steve Quinn (Senior Statistician, Flinders Clinical Effectiveness, Flinders University)
- A/Professor Donna Waters (Associate Dean, Research) Faculty of Nursing, Sydney University
- Health Economist: To be appointed

This committee is comprised of experts in the field of cardiology and the conduct of observational outcomes research. They will be responsible for scientific advice and recommendations on the:

- Scientific integrity of the registry
- Protocol and CRF
- Methodology to obtain the most representative population of participants and ensure good long term data quality;
- Implementation of the GRACE risk tool and treatment recommendation plan and process evaluation;
- Development of the overall operational guidelines for communication and publication;
- Collation of event reports to be assessed by the event adjudication committee;
- Governance over the academic analyses and publications derived from the protocol;
- Conduct of the Statistical analysis and the writing of the primary manuscript.

The committee will follow the status of the study by regular face to face meetings or teleconference during the registry.

Data management services will be provided by the Centre for Outcomes research (COR) at The University of Massachusetts Medical School, Worster MA USA. Data management will be responsible for data programming, query tracking and resolution, The COR web site is hosted within the secure UMMS Information Service environment that also houses statistical and graphics software. The front-end user-friendly interfaces use ASP.NET to support data storage and retrieval from the back-end SQL server database. Standards for HIPAA compliance include HTTPS protocol, 128 bit encryption, and individual Web login account. Data are organised in a structured format, and produce surveillance reports using query, search and analysis functions. Export features allow data to be extracted, in whole or in part, using Text, Excel and XML formats for further statistical analysis by the Steering Committee.

Coordination of the clinical event adjudication (CEA) process will be conducted via an independent Committee located at SAHMRI and the data Safety Monitoring Board will be a separate independent committee appointed and located at SAHMRI.

Support for the implementation of the GRACE risk tool and treatment recommendation plan will be coordinated by SAHMRI in cooperation with members of the Steering Committee.

a. Roles and Responsibilities of the study coordination centre

Training of study site personnel is the specific responsibility of the Study Coordination Centre at SLHD Concord Hospital and includes, overseeing the financial and regulatory aspects of the study, development of the case report forms**,** development of training manuals and audit procedures**;** tracking of data completion**,** resolution of data queries and monitoring data quality, and to perform data analysis for scientific publications.

b. Roles and Responsibilities of the Implementation Team

Study-resourced implementation managers led by SAHMRI will be responsible for implementing the study at each site, education of clinical staff involved and ensuring adherence to protocol specifications. Clinical champions will also need to be identified in order to directly engage and ensure the support of local ED and cardiology department clinicians. The study implementation managers will work closely with the study site to merge the risk stratification tool within current work practices. The study team will conduct training sessions to inform local clinical staff and study co-coordinators regarding the use of the tool. Qualitative descriptions of the local barriers and solutions experienced during the implementation of the tool at each site will be recorded to inform future efforts in generalizing the findings of the study. Time and resources required for implementation will be included in the cost effectiveness analysis.

c. Roles and Responsibilities of the Process Evaluation Team

A study-resourced process evaluation team co-located at the University of Sydney and the University of Adelaide will be responsible for the qualitative evaluation of the effectiveness of the implementation process at purposively selected sites. The methodology for this qualitative evaluation and interview questions will be submitted for ethical approval separately to selected centres.

d. Data Management

The project and data management will be based at the The Center for Outcomes Research (COR) at the University of Massachusetts Medical School (UMMS). Information collected will include baseline patient demographic and presentation characteristics, in hospital investigations, medical management and in-hospital outcomes. Data will be are collected electronically. The data protection standards at COR, currently meet all standards relating to the use of paperless records under the Good Clinical Practice regulations and comply with US Federal Information Systems policies including uniform policies, authorities, responsibilities, and compliance for System Security Planning within UMMS. This policy also provides guidance for developing system security plans in accordance with National Institute of Standards and Technology (NIST) Special Publication (SP) 800-18, "Guide for Developing

Security Plans for Federal Information System" and "NIST SP 800-53 The systems and procedures comply with the Electronic Records; Electronic Signatures; Final Rule: Electronic Submissions; Establishment of Public Docket; Notice of CRF 21 Part 11 of these regulations. Furthermore the systems and processes with respect to privacy and data protection comply with Health Records and Information Privacy Act (NSW) 2002 and Privacy Act (Cth)1988 and Australian Information Privacy Principles.

The COR web site is hosted within the secure UMMS Information Service environment that also houses statistical and graphics software. The front-end user-friendly interfaces use ASP.NET to support data storage and retrieval from the back-end SQL server database. Standards for HIPAA compliance include HTTPS protocol, 128 bit encryption, and individual Web login account. Data are organised in a structured format, and produce surveillance reports using query, search and analysis functions. Export features allow data to be extracted, in whole or in part, using Text, Excel and XML formats for further statistical analysis. The system is also compliant with the National E-Health Transition Authority (nehta) standard of reporting and storing data using a hierarchical structure of .pdf, XML and UML. These controls to maintain privacy and security of the data include measures designed to ensure the integrity of system operations and information stored in the system. Such measures include:

- Validation;
- COR generates accurate and complete copies of records;
- Archives and backs-up all records;
- Uses computer-generated, time-stamped audit trails;
- All staff who develop, maintain, or use electronic records and signature systems have the education, training, and experience to perform their assigned tasks.
- System access is limited to authorised individuals;
- Operational system checks are used to enforce permitted sequencing of steps and events
- Authority checks are used to ensure that only authorised individuals can use the system, electronically sign a record, access the operation or computer system input or output device, alter a record, or perform operations.

Checks are used to determine the validity of the source of data input or operation instruction; and written policies are established and adhered to holding individuals accountable and responsible for actions initiated under their electronic signatures, so as to deter record and signature falsification.

11. Clinical Event Adjudication Committee (CEAC) and Data and safety monitoring board (DSMB)

a. Clinical Event Adjudication Committee (CEAC)

The clinical endpoint adjudication committee (CEAC) will be chaired by a senior physician with extensive cardiac experience. All other committee members will be cardiology

consultants or fellows. The committee will be independent of all study investigators, sites, and the project and data management groups.

Source data required to confirm an event will first be sent in a de-identified format to the CEAC coordinator based at Concord Hospital. The documentation will be reviewed for completeness before the allocation of an event-specific Clinical Endpoint number which will replace all patient and institution codes on each source document, for that event, before submission to the CEAC. This process will ensure the CEAC remains blinded to both patient and institution identifiers. All event review requests and associated documentation will be submitted to the CEAC via a password-protecting portal.

The CEAC will review the followingevents (as required for the meta analysis on the international network of cluster randomised studies) .and associated source documents according to the requirements of the protocol, study timelines and following study specific standard operating procedures (SOPs):

- All deaths during hospital admission and at 12 months post discharge.
- All new / recurrent Myocardial Infarctions (including spontaneous and peri-procedural)

Should any communication be required with the site (eg. a request for additional information), this will be conducted via the CEAC coordinator to the coordination centre staff at Concord Hospital and then site.

b. Data Safety Monitoring Board (DSMB)

Within the scope of the Data Safety and Monitoring Board (DSMB) charter, this committee will ensure that no increase in adverse events associated with risk stratification using the GRACE risk-score intervention is introduced. The DSMB will consist of members who are external to the study and the CEAC. The DSMB will be constituted by 3 senior clinicians from non-participating hospitals and one (non-voting) statistician and will be chaired by an independent cardiologist.

When 50% of anticipated patients have been enrolled, the adjudicated clinical events will be forwarded to the DSMB following re-identification of the treatment arm by the CEAC coordinator. The DSMB will review the data to compare the number and type of events in each group and report on the findings. These results will be advised to HREC's and participating sites following each review.

In the event that there is a disparity between the groups then the DSMB may make a recommendation regarding the continued conduct of the study. The DSMB is responsible for safeguarding the interests of study participants, assessing the safety and efficacy of study procedures.

The DSMB reviews data generated by the study in a periodic basis and recommends one of the following actions to the Principal Investigator:

- Discontinue the study (with provision for orderly discontinuation in accord with good medical practice).

• Modify the study protocol. Modifications may include, but not limited to, changes in inclusion/exclusion criteria, frequency of patient follow up visits or safety monitoring, alterations in study procedures.
• Continue the study according to the protocol and any related amendments.

12. Ownership of the data and study results

Unless otherwise specified by local laws and regulations, the Sponsor (SLHD) together with the Steering Committee retains ownership of data, results, reports, findings, discoveries related to this study. Therefore, the Sponsor reserves the right to use the data from the present study for any purpose.

13. Publications

The final decision to publish any manuscript/abstract/presentation will be made by the Steering Committee.

All manuscript/abstract/presentation must be submitted to the Steering Committee for review at least forty-five (45) calendar days in advance of submission. Astra Zeneca may request that the Company's name and/or names of one or several of its employees appear or do not appear in such publication. This latter condition will be contingent upon the employee contributing sufficiently to the academic production of the manuscript as per the NHMRC publication guidelines for authorship.

14. Evaluation and calculation of variables

a. Clinical Characteristics during the index presentation

- Demographics (Initials,year of birth,and postcode gender**)**
- Medical history (angina; TIA/stroke; diabetes; Coronary Artery Disease; Myocardial Infarction; Percutaneous Coronary Intervention; Coronary Artery Bypass Grafting; positive stress test; Peripheral Arterial Disease; Atrial Fibrilliation; malignancy; major bleeding; renal failure; obstructive sleep apneoa), History of Depression
- Cardiovascular risk factors (previous cardiac history – from above; smoking status; hypertension; hyperlipidaemia; obesity; family history)
- Date and time of admission
- Date and time of symptom onset.
- Presenting clinical symptomatology
- Presumptive initial diagnosis
- Physician Predicted risk of ACS
- Serum cholesterol, creatinine, white cell count, haemoglobin, urinalysis (if performed by the hospital)

- In-patient therapies: procedures (echocardiography; exercise tolerance test; left ventricular ejection fraction; pacemaker; other)
- In-patient therapies: interventions (cardiac catheterisation; percutaneous coronary intervention; coronary artery bypass grafting; stenting; clinical trial; other)
- In-patient therapies: drug treatments (Thrombolytics – streptokinase, alteplase, reteplase, tenecteplase; Anti-Coagulants - unfractionated heparin, low molecular weight heparin, warfarin, dabigatran; Antiplatelets – GP IIb/IIIa, aspirin, $P2Y_{12}$ inhibition, unfractionated heparin, low molecular weight heparin, other; Other Medications – ACE inhibitor, angiotensin receptor blocker, calcium channel antagonist, beta blocker, statin, clinical trial, other)
- In-patient events (myocardial infarction – not as part of admitting reason; re-infarction; recurrent angina, congestive heart failure; cardiogenic shock; pulmonary oedema; acute renal failure; stroke – haemorrhagic and non-haemorrhagic; major bleeding; sustained ventricular tachycardia or ventricular fibrilliation)
- Medications at discharge (aspirin; warfarin; P_2Y12 inhibition; ticlopidine; ACE inhibitor; angiotensin receptor blocker; calcium channel antagonist; beta blocker; digoxin; diuretic; nitrate; statin; dabigitranm, rivaroxaban and apixaban; clinical trial; other)
- Place of discharge (home; transfer – acute care, rehabilitation, for procedure - specify, other)
- Date of discharge
- Primary discharge diagnosis (acute coronary syndromes; other cardiac diagnosis – specify; other).

b. Death and readmission for cardiovascular causes within 12 months

- Cardiovascular mortality
- Unplanned hospital admission for: non-elective coronary revascularization (PCI or CABG); cerebrovascular accidents with cerebral imaging; atrial or ventricular arrhythmias; (re) MI, CCF; as documented by a hospital discharge summary or diagnosis-related group report.
- Significant Bleeding
- Medications (aspirin; warfarin/other anti-coagulants; clopidogrel, prasugrel, ticagrelor; ACE inhibitor; angiotensin receptor blocker; calcium channel antagonist; beta blocker; digoxin; diuretic; nitrate; statin; clinical trial other)
- Receipt of secondary prevention
- Quality of life assessment

c. Quality of Life: EQ-5D Calculation or derivation of efficacy variable(s)

Quality of life measures using the EQ5D instrument will be collected at 1 year. Linkage to the PBS/MBS data and NHMMD will also be sought from consenting patients. Resource use from

the date of enrolment up to and including 1 month beyond the final assessment will be costed using MBS, PBS and AN-DRG cost weights.

d. Definitions of outcome variables

i. Cardiovascular Death

Cardiovascular Death will be defined as death due to myocardial infarction, sudden cardiac death, death due to heart failure or cardiogenic shock, stroke, and other causes including pulmonary embolism, or aortic aneurysm rupture.

ii. Myocardial Infarction

This study will implement the Third Universal Definition of myocardial infarction.(26) The appropriate definition of myocardial infarction will depend upon the clinical situation for which it is being applied. However, given the complexity in diagnosing myocardial infarction soon after the index event, suspected recurrent myocardial infarction will only be sought 18 hours after the time to presentation.

New MI

A myocardial infarction with evidence of myocardial necrosis in a clinical setting consistent with myocardial ischaemia that includes one of the following

- Detection of a rise and/or fall of biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit (URL) together with the evidence of myocardial ischaemia with at least one of the following;
  - Symptoms of ischaemia
  - ECG changes indicative of new ischaemia, new ST-T changes or new LBBB
  - Development of pathological Q waves in the ECG
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
- Sudden unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischaemia, and accompanied by presumably new ST elevation, or new LBBB, and /or evidence of fresh thrombus by coronary angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.
- MI post PCI - see below MI post intervention
- MI post CABG - see below MI post intervention

Pathological findings of an acute myocardial infarction

Re-MI

The definition of an MI, in those not undergoing revascularization procedures will depend on whether or not the admission diagnosis is unstable angina or MI. Admission MI will be diagnosed if any troponin, CK-MB (or CK in the absence of CK-MB) determination is

elevated >ULN within 12 hours of the most recent episode of chest pain that qualified the participant for the trial.

In participants <u>without</u> MI at admission, a MI after enrolment but prior to angiography will be diagnosed when:

- any elevation of troponin or CK-MB >ULN occurs (or CK >ULN in the absence of MB determination).

In participants <u>with</u> MI at presentation, in whom the elevated troponin or CK-MB (or CK) levels are documented to be falling or have returned to normal, diagnosis of a second infarction requires:

- a new elevation of troponin or CK-MB >ULN (or CK >ULN in the absence of MB determination) if the troponin or CK-MB (or CK) level has returned to <ULN, or
- a rise by >20% or 50% above the previous nadir level if the troponin or CK-MB (or CK) level, respectively, has not returned to <ULN.

In participants <u>with</u> MI at presentation, in whom the peak troponin or CK-MB (or CK) has not yet been reached, diagnosis of a second infarction requires:

(a) recurrent chest pain ≥30 minutes, or
(b) new ECG changes consistent with MI, and
(c) the next troponin or CK-MB (or CK) level measured approximately 8-12 hours after the event be elevated by at least 50% above the previous level.

iii. MI following PCI

Myocardial infarction associated with PCI requires an elevation of cTn values >5 x 99th percentile URL in patients with normal baseline values (>99th percentile URL) or a rise of cTn values >20% if the baseline values are elevated and are stable or falling.
In addition, either:

(i) Symptoms suggestive of myocardial ischemia, or (ii) new ischemic ECG changes or new LBBB, or
(ii) Angiographic loss of patency of a major coronary artery or a side branch or persistent slow- or no-flow or embolization, or
(iii) Imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.

Myocardial infarction associated with stent thrombosis is detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/ or fall of cardiac biomarkers values with at least one value above the 99th percentile URL.

iv. MI following CABG

In participants undergoing CABG, diagnosis of MI will require:

Myocardial infarction associated with CABG will require elevation of cardiac biomarker values >10 x 99th percentile URL in patients with normal baseline cTn values (>99th percentile URL).
In addition, either

(i) New pathological Q waves or new LBBB, or
(ii) Angiographic documented new graft or new native coronary artery occlusion, or
(iii) Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

v. New or Worsening Heart Failure

New or worsening heart failure will be defined as the change of 1 or more in the patients Killip Class, between the presentation Killip Class and the worst Killip class documented for the patient during their hospitalisation.

- Killip Class I-Absence of rales over the lung fields and absence of S3
- Killip Class II-Rales over 50% of the lung fields and the presence of S3
- Killip Class III-Rales over more than 50% of the lung fields
- Killip Class IV- Cardiogenic shock

Medical record information may be also used to determine the worst Killip Class: cardiac failure is defined as symptoms of heart failure requiring diuretics and objective evidence or clinical evidence of heart failure including;

- Bibasilar rales in 50% or less of lung fields or an S3 heart sound (criteria is the same as Killip Class II)
- Pulmonary oedema (criteria as Killip Class III) as evidenced by a chest X-ray with pulmonary congestion
- Cardiogenic shock. This includes Hypotension (a systolic blood pressure of less than 90 mmHg for an extended period usually more than 30 mins; end-organ hypoperfusion (cool extremities or a urine output of less than 30 ml/h, and a heart rate of greater than or equal to 60 beats per minute).

vi. Significant Bleeding

Clinically significant bleeding will be defined as any one of the following:

- intracranial,
- retroperitoneal,
- intraocular,
- Gastrointestinal / genitourinary bleeding requiring intervention (endoscopy/transfusion) or cessation of therapies
- access site haemorrhage requiring radiological or surgical intervention,
- ≥5cm diameter haematoma at puncture site,
- reduction in haemoglobin concentration of > 4g/dL without an overt source of bleeding,
- reduction in haemoglobin concentration of > 3g/dL with an overt source of bleeding,
- re-operation for bleeding,
- use of any blood product transfusion,
- bleeding leading to re-hospitalization or prolongation of hospitalization

and meeting the bleeding classifications for TIMI Major/ minor/ minimal/ GUSTO/ ACUITY

- TIMI Major/minor/minimal bleed Major: Overt clinical bleeding (or documented intracranial or retroperitoneal haemorrhage) associated with a drop in haemoglobin of greater than 5g/dl (50g/l) or a haematocrit of greater than 15% (absolute).
- Minor: overt clinical bleeding associated with a fall in haemoglobin of 3g/dL to 5g/dL (50g/l) or a haematocrit of 9% to less than or equal to 15% (absolute).
- Minimal: Any clinically overt sign of haemorrhage (including imaging) that is associated with a <3 g/dl decrease in the haemoglobin concentration or <9% decrease in the haematocrit

GUSTO Bleeding Classification(29)

- Severe or life-threatening: Either intracranial haemorrhage or bleeding that causes haemodynamic compromise and requires intervention
- Moderate: Bleeding that requires blood transfusion but does not result in hemodynamic compromise
- Mild: Bleeding that does not meet criteria for either severe or moderate bleeding

ACUITY Bleeding Classification(30)

- Intracranial or intraocular
- Reduction in Hb of ≥ 4.0 g/dL without an overt source of bleeding, or of ≥ 3.0 g/dL with an overt source of bleeding
- Use of any blood product transfusion
- Haematoma ≥ 5cm in diameter, re-operation for bleeding, access site haemorrhage requiring intervention

BARC Bleeding Classification(31)

- Type 1: bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalisation, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional
- Type 2: any overt, actionable sign of hemorrhage (e.g, more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria: (1) requiring nonsurgical, medical intervention by a healthcare professional, (2) leading to hospitalisation or increased level of care, or (3) prompting evaluation
- Type 3:
  Type 3a
  1. Overt bleeding plus hemoglobin drop of 3 to <5 g/dL* (provided hemoglobin drop is related to bleed)
  2. Any transfusion with overt bleeding

  Type 3b
  1. Overt bleeding plus hemoglobin drop ≥5 g/dL* (provided hemoglobin drop is related to bleed)
  2. Cardiac tamponade
  3. Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid)

4. Bleeding requiring intravenous vasoactive agents

Type 3c

1. Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal)
2. Subcategories confirmed by autopsy or imaging or lumbar puncture
3. Intraocular bleed compromising vision

- Type 4: CABG-related bleeding
  1. Perioperative intracranial bleeding within 48 h
  2. Reoperation after closure of sternotomy for the purpose of controlling bleeding
  3. Transfusion of ≥5 U whole blood or packed red blood cells within a 48-h period†
  4. Chest tube output ≥2L within a 24-h period
- Type 5: fatal bleeding

  Type 5a

  Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious

  Type 5b

  Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

vii. Stroke with documentation on imaging (eg CT or MRI) of

- **Haemorrhagic**: a stroke haemorrhage in the cerebral parenchyma or a sub-dural or subarachnoid haemorrhage.
- **Ischaemic**: documented history of stroke or cerebro-vascular accident (CVA) resulting from an ischaemic event where the patient suffered a loss of neurological function with residual symptoms remaining for at least 24 hours.

15. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

a. Determination of sample size

In the existing CONCORDANCE data set (n=6561), 2326 (36%) patients are classified as high-risk (GRS greater than 118). Among these, the mean use of guideline recommendations is 49.7%. If each of the three above indices of guideline adherence (use of coronary angiography, discharge on at least 4 of aspirin, statin, $P2Y_{12}$ inhibition, beta-blocker, ACE-inhibitor/ARB, and referral to any secondary prevention program) is given a score of one, (i.e. inpatient angiography=1, discharge on optimal medical therapy=1, rehabilitation referral=1) then a patient meeting all three indices of guideline adherence would have a total score of 3.

A sample size of 12 sites per group with 28 high risk patients per site achieves an 80% power to detect a difference in the total score of 0.5 between the group means when the standard deviation is 0.92 and the intra-cluster correlation is 0.176 using a Two-sided T-test with a significance level of 0.05.

Therefore, this study will enroll 28 high-risk patients per cluster or 336 patients per arm. However, it will be important to recruit all patients presenting with an ACS diagnosis regardless of risk as their management will also likely be influenced by the intervention and the benefits of some recommendations (like angiography) are not as well established in this group. The total samples size therefore will be 947 patients per arm or 1894 in total. Outcomes in this whole cohort will be assessed as a secondary endpoint.

Secondary endpoint (clinical events):

In the ACACIA study (conducted during 2006-7, 39 centres in Australia, many of whom have agreed to participate in CONCORDANCE for this study). In this study, 2704 patients were admitted with either STEMI or high-risk ACS and by discharge, 64 (2.5%) had died and 419 (15.9%) were not deemed to have an ACS diagnosis. Of those surviving to hospital discharge, 1053 (47.4%) died, suffered a recurrent MI, or required a cardiovascular readmission within 12 months. From our CONCORDANCE data, we estimated the ICC to be 0.0166.

By sampling 80 high-risk patients (GRACE score >118) from each of 12 hospitals in each group (24 hospitals in total), will achieve 80% power to detect a difference in the composite endpoint of 20% (48.0% in the usual care group vs. 38.0% in the intervention group) using a two-sided Z test (un-pooled), with a significance level of 0.050, and with the ICC set at 0.0166.

This would require a total sample size of approximately 2,664 in each group, beyond the capacity of the AGRIS study. To optimize the likelihood of detecting an effect on clinical outcome we plan a pre-specified meta-analysis combining data from this study and closely related Cluster RCTs being conducted in Canada, the United Kingdom and Asia.

b. Description of analysis sets

Primary analysis set

Primary Performance Measure Analysis: The primary analysis will compare the risk stratification using GRACE risk tool- and treatment recommendation plan versus standard therapy in improving the primary performance measure endpoint (application of all guideline recommended therapies at baseline). Given the heterogeneous population of patients who present with suspected ACS, combined with the difficulty in assessing application of guidelines among those patients who die in hospital, the primary analysis population will be confined to those patients discharged alive with an ACS diagnosis (STEMI, NSTEACS or unstable angina). Correlations between achievements of performance measures and late events will also use the primary analysis population.

Clinical Endpoint Analysis: The main analyses assessing the impact of risk stratification using GRACE risk tool on the primary clinical endpoint will be applied

to all patients who have not opted out of the study and have a GRACE risk score of >118 at the time of enrolment/admission.

Secondary analysis set

Secondary analyses of late clinical outcomes including cardiovascular mortality, recurrent MI, new or worsening heart failure and readmission for cardiovascular disease including bleeding events will use the entire study population who have not opted out of the study ie; entire intention-to-treat population.

Health economic analysis: quality-of-life, and cost-effectiveness analyses will be applied to all patients providing informed consent (for PBS and MBS data) at the time of enrolment.

c. Methods of statistical analyses

A flow chart showing the flow of patients through the trial and reasons for drop out or withdrawals will first be provided. The two groups will then be compared on baseline characteristics, with Chi-squared tests undertaken for categorical variables, and independent samples t-tests for continuous variables. Non-parametric analyses will be used where necessary. The primary analysis will compare the efficacy of risk stratification with GRACE-risk score intervention versus standard care in improving the primary performance measure endpoint in the population alive at the time of discharge and among patients with a GRACE score>118 for the primary clinical endpoint. To account for between-cluster variance, a GEE regression model with log link and binomial family will be used for this purpose. The initial analysis will simply compare composite outcome rates at 12 months between the two groups. Any variables in baseline analyses that differ between the two groups will then be included in the GEE model. The primary analysis will be on an intention to treat basis. Multiple imputations may be used to replace missing values if the assumptions appear to have been met.

Differences between the groups in freedom from mortality, recurrent MI and cardiac readmission (i.e. the individual components of the composite outcome)will be assessed by Cox proportional hazards model survival analysis. The relationship between clinical guideline adherence (as measured by performance indicators) and late clinical events among individual patients will also be evaluated in survival analysis.

Secondary outcomes including the interactions between the GRACE score use and hospital or clinical service characteristics, and ACS performance measures and late clinical outcomes will be examined using two-level random effects linear and logistic regression models respectively (STATA 12: xt commands). These models will include hospital level and patient level variables such as type of facility, number and qualification of medical staff, onsite invasive services, existing presence of clinical pathways etc. Given the small sample of hospitals included in this study, this component of the analysis will remain highly exploratory and will

have limited power to detect interactions between hospital characteristics and efficacy of decision support. Nevertheless, observations from this analysis will be used to inform future projects. All analyses will be undertaken using the STATA 12 statistical package.

d. Interim analyses

As there will be limited capacity to modify the study prior to completion, no formal interim analysis will be undertaken.

LIST OF REFERENCES

1. Huynh LT, Chew DPB, Sladek RM, Phillips PA, Brieger DB, Zeitz CJ. Unperceived treatment gaps in acute coronary syndromes. International Journal of Clinical Practice. 2009 Oct;63(10):1456–64.

2. Scott I, Derhy P, O'Kane D, Lindsay K, Atherton J, Jones M. Discordance between level of risk and intensity of evidence-based treatment in patients with acute coronary syndromes. Med J Aust. 2007 Aug 1;187(3):153–9.

3. Fox K, Anderson F, Dabbous O, Steg P, Lopez-Sendon J, de Werf Van F, et al. Intervention in acute coronary syndromes: do patients undergo intervention on the basis of their risk characteristics? The Global Registry of Acute Coronary Events (GRACE). Heart. 2007 Feb 1;93(2):177–82.

4. Hung J, Brieger DB, Amerena JV, Coverdale SG, Rankin JM, Astley CM, et al. Treatment disparities and effect on late mortality in patients with diabetes presenting with acute myocardial infarction: observations from the ACACIA registry. Med J Aust. 2009 Nov 16;191(10):539–43.

5. Joynt KE, Huynh L, Amerena JV, Brieger DB, Coverdale SG, Rankin JM, et al. Impact of acute and chronic risk factors on use of evidence-based treatments in patients in Australia with acute coronary syndromes. Heart (British Cardiac Society). 2009 Sep pp. 1442–8.

6. Majumdar S, Roe M, Peterson E, Chen A, Gibler W, Armstrong P. Better outcomes for patients treated at hospitals that participate in clinical trials. Arch Intern Med. 2008 Mar 1;168(6):657–62.

7. Astley CM, Macdougall CJ, Davidson PM, Chew DP. Lost in translation: health resource variability in the achievement of optimal performance and clinical outcome. Circulation: Cardiovascular Quality and Outcomes. 2011 Sep 1;4(5):512–20.

8. Granger C, Goldberg R, Dabbous O, Pieper K, Eagle K, Cannon C, et al. Predictors of hospital mortality in the global registry of acute coronary events. Arch Intern Med. 2003 Oct 1;163(19):2345–53.

9. Eagle KA, Lim MJ, Dabbous OH, Pieper KS, Goldberg RJ, de Werf Van F, et al. A validated prediction model for all forms of acute coronary syndrome: estimating the risk of 6-month postdischarge death in an international registry. JAMA. 2004 Jun 9;291(22):2727–33.

10. Fox KAA, Dabbous OH, Goldberg RJ, Pieper KS, Eagle KA, de Werf Van F, et al. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). BMJ. 2006 Nov 25;333(7578):1091.

11. Mehta SR, Granger CB, Boden WE, Steg PG, Bassand J-P, Faxon DP, et al. Early versus delayed invasive intervention in acute coronary syndromes. The New England journal of medicine. 2009 May pp. 2165–75.

12. 2011 Writing Group Members, Wright RS, Anderson JL, Adams CD, Bridges CR, Casey DE, et al. 2011 ACCF/AHA Focused Update of the Guidelines for the Management of Patients With Unstable Angina/ Non-ST-Elevation Myocardial Infarction (Updating the 2007 Guideline): A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2011 May 9;123(18):2022–60.

13. Chew DP, Aroney CN, Aylward PE, Kelly A-M, White HD, Tideman PA, et al. 2011 Addendum to the National Heart Foundation of Australia/Cardiac Society of Australia and New Zealand Guidelines for the management of acute coronary syndromes (ACS) 2006. Heart Lung Circ. 2011 Aug;20(8):487–502.

14. Authors/Task Force Members, Steg PG, James SK, Atar D, Badano LP, Lundqvist CB, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC). European Heart Journal. 2012 Aug 24.

15. Antman EM, Cohen M, Bernink PJ, McCabe CH, Horacek T, Papuchis G, et al. The TIMI risk score for unstable angina/non-ST elevation MI: A method for prognostication and therapeutic decision making. JAMA. 2000 Aug 16;284(7):835–42.

16. Morrow DA, Antman EM, Charlesworth A, Cairns R, Murphy SA, de Lemos JA, et al. TIMI risk score for ST-elevation myocardial infarction: A convenient, bedside, clinical score for risk assessment at presentation: An intravenous nPA for treatment of infarcting myocardium early II trial substudy. Circulation. 2000 Oct 24;102(17):2031–7.

17. Mehran R, Pocock SJ, Nikolsky E, Clayton T, Dangas GD, Kirtane AJ, et al. A risk score to predict bleeding in patients with acute coronary syndromes. Journal of the American College of Cardiology. 2010 Jun pp. 2556–66.

18. Subherwal S, Bach RG, Chen AY, Gage BF, Rao SV, Newby LK, et al. Baseline Risk of Major Bleeding in Non-ST-Segment-Elevation Myocardial Infarction: The CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines) Bleeding Score. Circulation. 2009 Apr 13;119(14):1873–82.

19. Chew DP, Huynh LT, Liew D, Astley C, Soman A, Brieger D. Potential survival gains in the treatment of myocardial infarction. Heart. 2009 Nov;95(22):1844–50.

20. Brieger D, Kelly A-M, Aroney C, Tideman P, Freedman SB, Chew D, et al. Acute coronary syndromes: consensus recommendations for translating knowledge into

action. The Medical journal of Australia. 2009. pp. 334–8.

21. Coiera E, Westbrook J. Should clinical software be regulated? Med J Aust. 2006 Jun 1;184(12):600–1.

22. Han Y, Carcillo J, Venkataraman S, Clark R, Watson R, Nguyen T, et al. Unexpected increased mortality after implementation of a commercially sold computerized physician order entry system. Pediatrics. 2005 Dec 1;116(6):1506–12.

23. Aliprandi-Costa B, Ranasinghe I, Turnbull F, Brown A, Kritharides L, Patel A, et al. The design and rationale of the Australian Cooperative National Registry of Acute Coronary care, Guideline Adherence and Clinical Events (CONCORDANCE). Heart Lung Circ. 2013 Jul;22(7):533–41.

24. Granger CB, Goldberg RJ, Dabbous O, Pieper KS, Eagle KA, Cannon CP, et al. Predictors of hospital mortality in the global registry of acute coronary events. Archives of Internal Medicine. 2003 Oct 27;163(19):2345–53.

25. de Araujo Goncalves P. TIMI, PURSUIT, and GRACE risk scores: sustained prognostic value and interaction with revascularization in NSTE-ACS. European Heart Journal. 2005 Mar 21;26(9):865–72.

26. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third universal definition of myocardial infarction. 2012. pp. 1581–98.

27. Kim J, Henderson RA, Pocock SJ, Clayton T, Sculpher MJ, Fox KAA, et al. Health-related quality of life after interventional or conservative strategy in patients with unstable angina or non-ST-segment elevation myocardial infarction: one-year results of the third Randomized Intervention Trial of unstable Angina (RITA-3). JAC. 2005 Jan 18;45(2):221–8.

28. Glasziou P, Simes R, Gelber R. Quality adjusted survival analysis. Stat Med. 1990 Nov 1;9(11):1259–76.

29. Rao SV, O'Grady K, Pieper KS, Granger CB, Newby LK, Mahaffey KW, et al. A Comparison of the Clinical Impact of Bleeding Measured by Two Different Classifications Among Patients With Acute Coronary Syndromes. J Am Coll Cardiol. 2006 Feb;47(4):809–16.

30. Stone G, McLaurin B, Cox D, Bertrand M, Lincoff A, Moses J, et al. Bivalirudin for patients with acute coronary syndromes. N Engl J Med. 2006 Nov 1;355(21):2203–16.

31. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. 2011. pp. 2736–47.

Intervention site

APPENDIX 1

Patient with ACS: positive ischaemic ECG/ troponin/ past history or new documentation of heart disease

Opt off consent to increase consecutive recruitment then study coordinator could approach patient during hospital admission for *opt in* consent to Medicare data

CLINICIAN DRIVEN BY DESIRE

TO DELIVER BEST PRACTICE CARE

- Leadership paramount from ED heads, ED senior MOs, cardiology heads, consultants on ward rounds etc
- Worksheet must add value in the clinical workflow

ED clinician:

4. Medical admission
5. Complete GRACE risk score and insert worksheet /sticker in the patient medical record and/or enter the score into the EMR
6. Refer to the decision-making pathway

Ward clinician:

1. Medical admission
2. Complete GRACE risk score and insert worksheet /sticker in the patient medical record and/or enter the score into the EMR
3. Refer to the decision-making pathway

STUDY COORDINATOR:

HREC Submission

Opt-out consent

EQ5D

Case record file

Source docs

Follow-up

EXTERNAL TRAINERS:

Site education regarding worksheet pivotal to be conducted by on-site by clinical leader (1x clinician and 1 x external trainer) with whole multidisciplinary team- nursing, medical, senior and junior, pharmacists, cardiac rehab during the regular site clinical meetings

External trainers would also have a monitoring role, regular site catch-ups over phone with PI etc to drive leadership