

Proposal for the Establishment of the Pan-Asian Resuscitation Outcomes (PAROS) Clinical Research Network

Abstract

Background

Resuscitation of emergency medical conditions and Out of Hospital Cardiac Arrest (OHCA) is a global health concern.

Design

A prospective, international, multi-center cohort study of out-of-hospital cardiac arrest across the Asia-Pacific.

Objectives

1. Describing regional variations in the incidence and outcomes of Out-of-Hospital Cardiac Arrest (OHCA) across Asia and beyond
2. Describing the true population based incidence of OHCA across different countries, using standardized common denominators as agreed across the network
3. Comparing Emergency Medical Services (EMS) outcomes (including response times and treatment outcomes) for OHCA across regions, allowing for international benchmarking and study of best practices
4. Understanding the etiology and preventable risk factors for OHCA and predictors of survival. The large sample size and international nature of the study will allow analysis of the influence of racial, population age structure, chronic disease burden, socio-economic factors, EMS characteristics, bystander cardio-pulmonary resuscitation (CPR), EMS response times, prehospital defibrillation and treatment, seasonal, geographic and climatic factors on OHCA incidence and outcomes.
5. Understanding geospatial and temporal occurrence of OHCA across regions that will facilitate systems level strategies for Public Access Defibrillation, community education and CPR training.
6. Study differences in the occurrence of OHCA between North American and Asia-Pacific populations, specifically with regards to the role of primary ventricular arrhythmias in sudden cardiac arrest.

Methods

Data will be collected from emergency dispatch records, ambulance patient case notes, Emergency Department (ED) and in-hospital records. All completed data will then be collected and sent to the Study Co-ordination Center for data management using Electronic Data Capture (EDC).

Eligibility

All OHCA presenting to EMS '995' and Emergency Departments during the study period as confirmed by the absence of pulse, unresponsiveness and apnea. Exclusion criteria will be those patients who are immediately pronounced dead, and for whom resuscitation is not attempted.

BACKGROUND

Resuscitation of emergency medical conditions and Out of Hospital Cardiac Arrest (OHCA) is a global health concern. Asia-Pacific's population is still increasing and is expected to age progressively in the next 10 to 15 years. Emergency medical conditions in the elderly are anticipated to increase and place greater demands on Prehospital Emergency Care (PEC) resources.

For example, of the approximately 16, 000 deaths that occur in Singapore every year, about 23% will be from a cardiac cause¹, of which, some 30-40% will occur suddenly, outside of a hospital. The mechanism of death is usually a fatal arrhythmia, most often ventricular tachycardia or fibrillation². Most of these patients die before ever reaching a hospital.

Currently, research into Prehospital Emergency Care (PEC) in Asia is inadequate. There is little collaborative research for PEC ongoing in the Asia-Pacific. Worldwide, there is wide regional variation in OHCA rates and outcomes reporting³. The International Liaison Committee on Resuscitation (ILCOR) suggests that OHCA should be a reportable health outcome⁴ and advocates a standardized reporting in the 'Utstein style'⁵. The Utstein style is a standardized reporting format for OHCA that has been adopted by ILCOR.

Early initiation of treatment has an important effect on outcomes and survival⁶. This is illustrated by the 'chain of survival' concept⁷ for cardiac arrest patients. This concept states that early initiation of the four 'links' in the chain of survival, will all improve survival in out-of-hospital cardiac arrest (OHCA). The links are 'early access' activating the Emergency Medical Systems (EMS) system by calling medical dispatch or 995, 'early Cardio-Pulmonary Resuscitation (CPR)', 'early defibrillation' delivering electrical therapy to restore a pulse and 'early advanced care' (airway management and drugs etc). Research has shown that for every minute OHCA is left unattended, chances of survival will decrease by 10%⁸. There is currently good research that indicates survival can be improved with shorter ambulance response times⁹⁻¹², early CPR^{6, 13} and early defibrillation¹⁴⁻¹⁷.

Understanding regional, geographical and temporal variations in the incidence of OHCA can also allow public health and systemic interventions to be more cost effective and targeted. An example is using geographical cardiac arrest occurrence to guide strategies for public access

defibrillation¹⁸. A large randomised controlled trial in the USA has shown the potential of such a strategy to improve survival outcomes¹⁹. A better understanding of the aetiology and predisposing factors for OHCA in Asian populations (compared to Western populations) could also guide prevention strategies and risk factor modification measures.

There is an urgent need for research and good quality interventional trials in PEC and OHCA in particular. The Cardiac Arrest and Resuscitation Epidemiology (CARE) study, is a multi-agency, Singapore -wide collaboration to study OHCA²⁰ which may serve as a model for a Pan-Asian Resuscitation Outcomes Network. Another example of a clinical research network (CRN) focused on Resuscitation is the Resuscitation Outcomes Consortium of North America^{3, 21, 22} and the Cardiac Arrest Registry to Enhance Survival (CARES)²³.

Specific objectives the PAROS study will address include:

1. Describing regional variations in the incidence and outcomes of Out-of-Hospital Cardiac Arrest (OHCA) across Asia and beyond

Are there regional variations in the incidence and outcomes of OHCA in the Asia Pacific, and what might these differences be due to?

So far, there have not been any population based, large scale studies of OHCA across the Asia-Pacific. Internationally, there has only been one prospective, population based multi-center study of note from North America³. From this and other retrospective reviews of OHCA across different EMS systems²⁴, we know that startling variations exist in the incidence and outcome of OHCA in North America alone. Survival for EMS-treated out-of-hospital cardiac arrest in North America varies approximately 12-fold for all-rhythms arrests (1.8—21.5%) and arrests presenting with ventricular fibrillation (3.3—40.5%)²⁵⁻²⁸. It would not be surprising to find that such variations exist in the Asia Pacific as well.

Variations in the incidence of OHCA might be due to underlying population differences as well as predisposing factors and chronic disease burdens. The commonest mechanism of death in OHCA is a fatal arrhythmia, most often ventricular tachycardia or fibrillation²⁹. This is related to coronary artery disease and various cardiovascular risk factors. Understanding regional variations in OHCA incidence and preventable risk factors might give impetus for public health interventions and provision of Prehospital Emergency Care resources.

In contrast, variations in OHCA outcomes are related not only to individual disease factors, but also to variations in EMS systems, practices, provider levels and population factors such

as bystander CPR and defibrillation²². Regional variations in outcomes provide an opportunity to examine the relationship of outcomes to EMS structural factors and might identify key components of EMS systems that are related to outcomes. System-wide efforts can then be addressed towards EMS elements that would have the most impact on outcomes. Finally, as PAROS will be sharing a common data taxonomy with ROC²² and CARES²³, there is an opportunity for comparison of data across the globe. This could be a unique opportunity to access such a large, international database for an important public health problem.

2. Describing the true population based incidence of OHCA across different countries, using standardized common denominators as agreed across the network

What is the true population based incidence of OHCA across the different countries?

A problem with much cardiac arrest research in the literature currently is that they represent opportunistic surveys of OHCA rather than a true population based approach³. A population based

assessment of the true burden of out-of-hospital cardiac arrest and potential characteristics that improve survival would be a key public health tool. Population-based data of out-of-hospital cardiac arrest will establish a baseline and enables assessment of subsequent evidence-based resuscitation

in community-based practice. It might help to establish novel prognostic measures that may serve to

further the understanding of the pathophysiology or guide patient care.

Another problem in the current literature and in practice is that different countries and EMS systems use different denominators for reporting outcomes. This may partially account for differences in reported survival rates in the literature^{22, 30}. Depending on the report or community, the denominator may consist of only cases initially presenting with ventricular fibrillation, EMS-treated cases regardless of presenting rhythm, or all cases of EMS-attended arrest consisting of those who are treated and those where resuscitation is not attempted. This makes it extremely difficult to make meaningful comparisons between EMS systems and countries.

We will standardize these definitions across the PAROS network by adopting by consensus a common taxonomy and data collection methodology. This will allow valid comparison of population based incidence and outcomes across network sites. In addition, sharing a

common taxonomy with the ROC and CARES study will facilitate a comparison with large sample, North American studies, using common denominators.

3. Comparing Emergency Medical Services (EMS) outcomes (including response times and treatment outcomes) for OHCA across regions, allowing for international benchmarking and study of best practices

What are the ‘best practices’ in EMS system design, operation, response times, treatment, data collection and post resuscitation practices? Are there ‘benchmarks’ that can be established among EMS providers that can be adopted by all?

There is currently little research describing the vast variation that exists in EMS systems internationally. This has a direct impact on the variation of OHCA outcomes seen in various studies²⁴⁻²⁸. Describing the spectrum of EMS services across our study sites will give insights into subsequent comparison of outcomes, and might highlight best practices³¹. These best practices could even evolve into ‘benchmarks’ that EMS systems can set for improving quality of services.

For example, Becker et al had proposed using the population incidence of cardiac arrest to correlate to predicted survival rates from cardiac arrests³² (see Figure 1). Thus EMS systems might be able to benchmark themselves as having ‘more cardiac arrest survivors than expected’ or having ‘fewer cardiac arrest survivors than expected’.

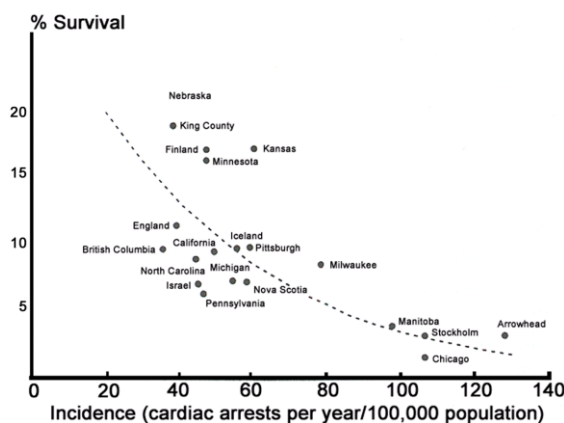


Figure 1: Normogram relating population incidence of cardiac arrest with predicted survival

4. Understanding the etiology and preventable risk factors for OHCA and predictors of survival. The large sample size and international nature of the study will allow analysis of the influence of racial, population age structure, chronic disease burden, socio-economic

factors, EMS characteristics, bystander cardio-pulmonary resuscitation (CPR), EMS response times, prehospital defibrillation and treatment, seasonal, geographic and climatic factors on OHCA incidence and outcomes.

What are the risk factors for OHCA? Are there modifiable predictors of survival from an individual level and from a system/public health perspective? Are there characteristics to identify 'at risk' populations which might require targeted intervention? Are there seasonal or circadian patterns to OHCA and what might this be due to?

Previous studies have suggested that there may be racial factors affecting the incidence and subsequent survival from OHCA³³. Certainly population characteristics and chronic disease burdens may be related to population incidence of OHCA, and this seems related to eventual survival rates³². The large sample size and international nature of the study will allow analysis of the influence of racial, national, population age structure, chronic disease burden and socio-economic factors etc on OHCA incidence and survival. This may help in understanding possible modifiable risk factors in populations, from an individual and public health perspective. Also, it can help to identify characteristics of 'at risk' populations, and help in the planning and provision of services for these populations.

From a system point of view, North American studies have identified several modifiable factors that predict survival from OHCA^{15, 34}. These include bystander CPR rates, time to defibrillation, EMS response time and initial presenting rhythm among others. Our study will look at the impact of such system factors on OHCA survival, and the components in each national EMS system that might be amenable for possible intervention to improve survival.

A number of acute cardiovascular events including acute myocardial infarction, cardiac arrest, and stroke have definite time distribution patterns rather than occurring as random events.³⁵ For example, it has been proposed that sudden cardiac arrests follow a circadian pattern³⁶⁻³⁹, with an increasing incidence in the mornings until noon^{35, 40}. Weekly patterns have also been noticed, with increased frequency of cardiac events on Mondays⁴¹⁻⁴⁴. We aim to see if there is indeed a circadian pattern that occurs and whether there are regional variations. This may have implications in understanding the underlying physiology as well as possibly affecting EMS and ED staffing and deployment.

Seasonal patterns have been observed for acute myocardial infarction^{45, 46} and sudden death⁴¹ in temperate climates. A higher volume of myocardial infarction cases have been reported in winter than in summer^{45, 46}. Similarly, a higher incidence of cardiac arrests during winter has been observed⁴¹. However it is currently unclear if this is a climatic effect or due to other factors. Describing the seasonal pattern of cardiac arrests across the northern, southern

hemisphere and in an equatorial location might shed light on whether this observation is due to a climate effect.

Identification of specific patterns in the occurrence of OHCA is of scientific importance because such patterns imply that there are external triggers to such events. A number of studies have suggested that there is a seasonal pattern to cardiac deaths in the United States⁴⁵,⁴⁶, Australia⁴⁷, and England⁴⁸. Theories that have been proposed to explain an increased prevalence of cardiac deaths in winter including cold weather affecting arterial blood pressure⁴⁹, arterial spasm, platelet and red blood cell counts, blood viscosity⁵⁰, plasma fibrinogen, factor VII⁵¹ and serum cholesterol levels⁵². Exposure to the cold also has important hemodynamic effects, including an increase in systemic vascular resistance, myocardial oxygen consumption and body metabolism⁵⁰.

5. Understanding geospatial and temporal occurrence of OHCA across regions that will facilitate systems level strategies for Public Access Defibrillation (PAD), community education and CPR training.

What is the geospatial and temporal distribution of OHCA across the region? Can we devise targeted strategies for community CPR training and PAD based on actual risk of OHCA in higher risk communities?

It has been noticed that cardiac arrests have definite time-geographic distribution patterns³⁵,⁵³,⁵⁴. This is related to the underlying population demographics and movement patterns. Using Geographic Information Systems (GIS) technology, we are able to depict such time-geographic patterns to aid planning for cardiac arrest interventions, such as PAD. GIS is multi-layering mapping software that is able to portray multiple geographic-time information in an easy to read, graphical manner.

There is currently good evidence that indicates the importance of delivering early defibrillation (< 4 mins)¹⁴⁻¹⁷. It has been pointed out that it would be prohibitively expensive and logistically difficult for ambulances to respond within 4 mins for every OHCA. With the invention of the simple-to-use automated external defibrillator (AED), it has been found that even untrained bystanders can successfully deliver life-saving defibrillation⁵⁵. This is the principle behind Public Access Defibrillation (PAD), which has shown great potential to increase cardiac arrest survival rates¹⁴,¹⁹,⁵⁶,⁵⁷. These programs empower laypersons to perform life-saving early defibrillation by making AEDs available in public places¹⁸,⁵⁸. Programs have been described, successfully placing AEDs at casinos¹⁴, and airports⁵⁹,⁶⁰.

We intend to use GIS to depict the geospatial distribution of OHCA across the region. This will facilitate plans for subsequent interventional trials utilizing targeted CPR training and PAD programs across communities. We intend to conduct a randomized trial by communities, comparing CPR alone and CPR with PAD in targeted communities. PAD will be augmented by web-based technology that will be able to send the nearest location of AEDs via cellphone to lay rescuers attending to a cardiac arrest.

6. Study differences in the occurrence of OHCA between North American and Asia-Pacific populations, specifically with regards to the role of primary ventricular arrhythmias in sudden cardiac arrest.

Are there differences in the presentation of OHCA between North American and Asia-Pacific populations? Are there differences in the demographics, etiology, underlying chronic disease burden and presentation?

One observation from current literature has been the relatively lower incidence of ventricular fibrillation (VF)/ ventricular tachycardia (VT) in Asian populations compared to North American ones. Asian studies have tended to report lower rates of VF ranging from 8-19%⁶¹⁻⁶⁴ and the commonest presenting rhythm is asystole. This is compared to 23-56%^{3, 28} presenting with VF in North American populations. Is this a true difference (not due to reporting methods) and could this be due to differences in the presenting population or etiology. If so, a difference in etiology may require different strategies for treatment. For example, a 'shock first' strategy is recommended for VF, while this strategy would be futile for asystole, and good initial CPR is required instead.

A CRN is a group of clinical, research, and administrative professionals organized to design, conduct, analyze and publish multi-site clinical, translational, or services research studies. The CRN has pre-established fiscal, legal, administrative, and management agreements and procedures so that when a protocol is established, an accurate, rapid budget estimate can be made, clinical professional staff are trained and in place and potentially contentious issues (e.g. Intellectual Property [IP], authorship, data ownership, Clinical Trial Agreement [CTA] specifics, etc.) have been resolved.

We believe that establishing such a network in the Asia Pacific will give valuable information regarding OHCA in Asia Pacific countries, and will help to develop an understanding of the variations among different emergency medical systems in the Asia Pacific. Such a network

can provide a platform to support and stimulate research into the most effective strategies to improve survival from sudden cardiac arrest (SCA) and other prehospital emergency conditions. Such efforts will require multi-pronged strategies targeting the community, Emergency Medical Services (EMS) and the hospitals. In brief, a Pan-Asian Resuscitation Outcomes Network will be important to track trends and conduct clinical trials on the effectiveness of subsequent interventions related to our EMS systems.

OBJECTIVES

1. To establish a Pan-Asian Resuscitation Outcomes Clinical Research Network, that will provide user-friendly clinical research infrastructure, to conduct patient-oriented clinical, translational or services research in a high quality yet cost-efficient manner.
2. To conduct a Pan-Asian descriptive study of Prehospital Emergency Care systems that will establish a basis for systems-wide comparison of resuscitation outcomes across the Asia-Pacific.
3. To conduct a national Cardiac Arrest Resuscitation Outcomes Study in Singapore as part of a Pan-Asian Resuscitation Outcomes comparative study. The PAROS CRN is in turn linked to the Cardiac Arrest Registry to Enhance Survival (CARES) funded by the Centers for Disease Control, Atlanta, USA.
4. Increase efficiency of contracting, paying for, executing, completing and publishing Patient Oriented Research (POR) for both Investigator Initiated and Industry Initiated studies.
5. Create a competitive business and scientific edge in the Asia-Pacific to successfully cooperate with others.
6. Improve the quality, impact and international recognition of POR for the Asia-Pacific.

Specific objectives this international study will address include:

1. Describing regional variations in the incidence and outcomes of Out-of-Hospital Cardiac Arrest (OHCA) across Asia and beyond
2. Describing the true population based incidence of OHCA across different countries, using standardized common denominators as agreed across the network
3. Comparing Emergency Medical Services (EMS) outcomes (including response times and treatment outcomes) for OHCA across regions, allowing for international benchmarking and study of best practices

4. Understanding the etiology and preventable risk factors for OHCA and predictors of survival. The large sample size and international nature of the study will allow analysis of the influence of racial, population age structure, chronic disease burden, socio-economic factors, EMS characteristics, bystander cardio-pulmonary resuscitation (CPR), EMS response times, prehospital defibrillation and treatment, seasonal, geographic and climatic factors on OHCA incidence and outcomes.
5. Understanding geospatial and temporal occurrence of OHCA across regions that will facilitate systems level strategies for Public Access Defibrillation, community education and CPR training.
6. Study differences in the occurrence of OHCA between North American and Asia-Pacific populations, specifically with regards to the role of primary ventricular arrhythmias in sudden cardiac arrest.

PRELIMINARY STUDIES/PROGRESS REPORTS

This study will be a continuation and expansion of the work of the Cardiac Arrest and Resuscitation Epidemiology in Singapore (CARE). The CARE study group includes representatives from the 6 major public hospitals in Singapore, the Singapore Civil Defence Force, Health Sciences Authority and the Clinical Trials and Epidemiology Research Unit, Singapore. CARE phase I found survival from out-of-hospital cardiac arrest (OHCA) in Singapore to be 2.0%⁶⁵. Mean (S.D.) EMS response time was 10.2 (4.3) minutes. Mean (S.D.) time from call to defibrillation was 16.7 (7.2) minutes.

In subsequent phases, the group has looked at the effect of various interventions in cardiac arrest⁶⁶⁻⁶⁸, cardiac arrest in specific situations^{69, 70} and community attitudes towards cardiac arrest⁷¹⁻⁷³. Recently, we completed a study describing the geographic epidemiology of prehospital cardiac arrest in Singapore⁷⁴.

We intend to use the methodology honed during the CARE study as a model for establishing a Pan-Asian Resuscitation Outcomes study. The Asian EMS Council was established in 2009 and has adopted the PAROS study as one of its core activities in the next 5 years. The Principal Investigator of the proposed PAROS study is the current Vice Chairman and Chairman elect (2010) of the Asian EMS Council. So far, a total of 10 countries across the Asia-Pacific have committed to this study (see appendix 1). In addition, the Korean Centers

for Disease Control has already committed USD \$1,000,000 for the portion of the study to be done in Korea.

We have also collaborated with the Resuscitation Outcomes Consortium of North America^{3, 21, 22} and the Cardiac Arrest Registry to Enhance Survival (CARES) (Centers for Disease Control, Atlanta, USA)²³ to come up with a unified taxonomy and data dictionary for the study. In addition the CDC Atlanta, USA has promised technical support for the study, including assistance in setting up a server based in Singapore running the Electronic Data Capture (EDC) platform.

METHODS

We propose to establish a Pan Asian network of EMS physicians that will collect and link data and outcomes from OHCA and other prehospital emergencies in their respective cities and countries, to include EMS data from dispatch services, ambulance records and service providers. In addition, data regarding cardiac arrest outcomes and other conditions will be collected from all major hospitals. This effort should be done in conjunction with hospital appointed ‘champions’, including physicians and nursing personnel interested in the field of sudden cardiac arrest and prehospital emergency care.

Study design

A prospective, international, multi-center cohort study of out-of-hospital cardiac arrest across the Asia-Pacific.

This proposal will fund the portion of the study to be conducted in Singapore and to set up the trial coordinating center in Singapore. Each participating country will be expected to raise the funding required for their own local portion of the study.

Patient eligibility

- All OHCA presenting to EMS ‘995’ and Emergency Departments during the study period as confirmed by the absence of pulse, unresponsiveness and apnea.
- Exclusion criteria will be those patients who are immediately pronounced dead, and for whom resuscitation is not attempted, including decapitation, rigor mortis and dependent lividity.

Variable measured

Definitions will follow Utstein recommendations⁷⁵ as well as conform to a unified taxonomy established by the PAROS steering committee (see appendix 2).

Outcome variables:

- Any return of spontaneous circulation
- Admitted to ICU/ward
- Discharged alive
- Glasgow Outcome Score (Cerebral Performance Category and Overall Performance Category) (see appendix 3)

System variables:

See appendix 4 for a sample of the Case Record Form (CRF)

Logistics

Data will be collected from emergency dispatch records, ambulance patient case notes, Emergency Department (ED) and in-hospital records. All completed data will then be collected and sent to the Pan-Asian Resuscitation Outcomes Study Co-ordination Center for data management using Electronic Data Capture (EDC). The EDC is an online, data registry system that will be set up with assistance from the Singapore Clinical Research Institute's (SCRI) / Duke-NUS Graduate Medical School / Singapore General Hospital.

GOVERNANCE AND MANAGEMENT OF THE CRN

The management of the CRN is envisioned to be undertaken by a CRN Executive Committee. The Executive Committee will provide direction and be the decision-maker on all major issues pertaining to the acceptance, management, budgeting, conduct, authorship and publication of trials or other CRN studies. These arrangements and agreements will be set forth before the CRN embarks on each new study, and will be transparent to everyone involved with the Network as well as to sponsor(s).

Executive Committee

The Executive Committee Chair and Co-Chair will be recognized disease experts in the Asia Pacific with established publication records and expertise in the conduct of multi-site trials.

The Chair and Co-Chair may or may not also function as the Study Principal Investigator (PI) and Co-PI for particular studies. The Executive Committee will also comprise all Asia Pacific Clinical Site PIs. The CRN will also have the autonomy to decide to rotate persons who serve as Executive Committee, Chair or Co-Chair (i.e. Network PI and Co-PI). In addition, the Executive Committee will include the Network Biostatistician, SCRI CEO or designee, and a Clinical Research Network Clinical Manager, and depending on need a CRN Administrative Manager.

The Executive Committee will be served by two additional committees, which will be specific for each study conducted through the CRN: the Publication Committee, and the Operations Committee.

Publication Committee (PC)

A PC will be designated for each study by the Executive Committee. The PC will have 6-8 members including the Study Biostatistician, and in general, more junior as well as selected senior investigators are encouraged to serve on the PC.

The PC is chaired by the Study PI or Co-PI and Co-Chaired by the Study Biostatistician. This committee oversees reviews, provides written critiques, and gives final approval for all journal article submissions from the study. It also designates materials that go on the public section of the study Website and, depending on the Executive Committee, may or may not provide authorization for any poster or other public presentation of the primary study, secondary analyses, or ancillary studies.

The PC may contract with a medical writer when needed, though the first author of any manuscript must write the first draft. Once a manuscript is submitted, correspondences are between the corresponding author and the journal. Final versions of the manuscript, if revisions are required, must go through and receive approval from the Publication Committee.

The PC proposes the rules of authorship to the Executive Committee OR the Executive Committee and Study PI establish the rules of authorship, in either case before study initiation. The general guidance is that for multisite studies, the Study PI and Co-PI, the Study Biostatistician, Assistant Biostatistician and/or Data Manager, Project Manager, and all

site PIs are co-authors. Site Co-PIs will be included whenever the position is earned and is feasible given publication limitations.

Secondary analyses are typically assigned to Clinical Site PIs or Co-PIs. In these cases, the Study PI and Co-PI become senior authors. These publications continue to include the Biostatistician and other Data Center (i.e. SCRI) personnel involved in study management if they have made substantive scientific contributions to the manuscripts. Specific numbers and types of slots for co-authors will be stipulated prior to study initiation for the primary and planned secondary analyses. The PC (or the Executive Committee – depending on the Network and Study) will review, approve and recommend author slots for additional (unplanned) secondary analyses.

Operation Committee (OC)

The Operations Committee will be Co-Chaired by the Study Co-PI and the Head of the Data Center (Head of Research Operations at SCRI or his designee). The Committee will include the Clinical Research Network Clinical Manager, a Study Project Manager, possibly a regulatory person and possibly an Administrative Manager others. The role of the OC would be to oversee and make decisions (or provide recommendations to the Executive Committee) pertaining to all operational aspects of running the study, e.g. issues pertaining to data management, study monitoring and regulatory considerations.

STUDY MANAGEMENT PROCESS

The CRN will decide on the selection of clinical sites for the network, and determine recruitment and training needs. The SCRI Research Informatics task Force will also support the CRN by making recommendations on the appropriate Information Technology systems and their functionalities.

The CRN will define other study management processes based on the needs of the network, to include but not limited to issues such as meeting frequency and study termination. Other critical processes such as adverse events reporting, Institutional Review Board (IRB) reports and ethics requirements shall be defined to comply with Good Clinical Practices (GCP) guidelines and institutional / national level regulatory requirements.

NETWORK POLICIES

Specific operational policies will be developed by the CRN Executive Committee. But following general guidance may be used or adapted as appropriate.

Data Ownership & Analyses

Investigator initiated studies that use the network will have a Study PI. The Study PI will be a Network member. The data generated from the study belong to the Network. If the Study PI chooses to leave the Network, the study data remain with the Network and continue under SCRI management. Data analyses by clinical sites on their own exclusive study data are not allowed. If a Site PI wishes to conduct data collection in addition to the designated formal work conducted at that Site (with or without collaboration of other clinical Sites), such an effort constitutes an Ancillary Study (see below).

Secondary Data Analyses

The designation of secondary data analyses will be made both at primary study initiation and at primary study conclusion. Secondary analyses must be supported by funds included either in the original budget or obtained as supplemental budget. Secondary analyses can be managed by an Ancillary Study Committee (ASC) or by the Executive Committee depending on the size of the Network/ Study, and the Network Executive Committee. Authorship policies for the primary and expected/planned secondary analyses will be established prior to study initiation.

Data Release to Clinical Site PIs

The Network Executive Committee will establish rules for each study as to when the study data set can/will be released to Clinical Site PIs. The general principle, so as to ensure the promotion of the scientific careers of the Study and Clinical Site PIs and Co-PIs, as well as to reduce cost, is to conduct all major analyses at the Network Data Center (i.e. SCRI). It is easier for the data analyst/statistician who is familiar with the data set to conduct the analyses.

Intellectual Property (IP) Issues

Most studies on most networks carry no implications or issues for IP. For each study on the network, however, the proposed protocol will clarify whether IP issues are present or not. If present, or possibly present, the IP issues will be discussed at the Executive Committee and

ultimately across all Clinical Site PIs. Legal counsel, if needed, will be sought (via SCRI support).

Network membership

The membership to a CRN will be defined by its Executive Committee on the basis of participation which will be reviewed annually. The participation refers mainly to contribution of patients but may also include contributions to study protocol, and other inputs to the study/network.

It is important that the Executive Committee members have the interest, expertise, as well as ability to contribute to each CRN. Hence continued membership is dependent on contribution to various aspects of the CRN's roles. For example, a clinical site PI would be expected to contribute a minimum number (to be decided by each CRN) of patients to any trials conducted by the network trial in a 3-year period. Alternatively but not exclusively, Executive Committee members could also contribute to clinical trial design, funding or management. Executive Committee members would be allowed to fully participate in the decision making process of the CRN.

While any clinical members of the Committee may propose a new study, Study PI who has proposed the study would be expected to secure the required funding to conduct the study. In the absence of such funding, the CRN has no obligation to proceed with the trial.

It is envisaged that there will be two types of memberships:

- a. Ordinary members: any clinician who has enrolled three or more patients into any clinical trial conducted by the CRN. They will be invited to attend General Meeting or Scientific Meetings of the CRN.
- b. Associate members: interested individuals who may be clinicians, para-clinicians, scientific staff or lay individuals. These will be kept on a mailing list to receive updates of the activities of the CRN. They may be allowed to attend General Meetings or Scientific Meetings of the CRN subject to the Executive Committee's approval.

INITIAL WORKPLAN

The initial task of the network will be to propose and agree upon a common taxonomy and data dictionary for reporting out-of-hospital cardiac arrest (OHCA). This task has already been initiated in collaboration with the Resuscitation Outcomes Consortium (ROC) of North America. We aim to have a working draft by September 2009, to be compiled into a proposed case record form (CRF) to be adopted by all member institutions.

The first project aimed for publication will be a general survey of all participating sites, to be rolled out in March 2010. An Operation Committee and Publication Committee will be established for this project. The aims of this survey will be to publish an Asia-Pacific wide description of current EMS systems, including underlying population demographics, system characteristics, organizational and baseline characteristics. This effort will define the network and establish the administrative and management functions. It will provide an initial publication to document the scientific credibility of the group and describe system characteristics which will contextualize future patient orientated research outcomes.

A secondary aim of the survey will be to collect information on network site's current data collection systems and databases in relation to the proposed standardized taxonomy. By the end of the first project which should be completed by end 2010, the network will have established each member site's capability with regard to data collection. This 'run-in' period will also allow each member site time to align to the uniform reporting and data collection procedures.

In parallel to these efforts, the network will set up an EDC system, which will be web-based, for easy access of all member sites. The EDC will be set up beginning in mid January 2010, with a training planned to launch in mid March 2010. A major training effort for the EDC will coincide with the next meeting of the network executive committee in June 2010, on the sidelines of the International Conference on Emergency Medicine.

The EDC will support the network's 2nd project, which will be a network wide comparative study of OHCA management and outcomes in the Asia-Pacific. This will be launched in June 2010 and will aim for completion in June 2011. In the interim, the group will meet to define

the next investigator-initiated project, with the aim of conducting interventional randomized controlled trials for OHCA in our network.

Statistical considerations

Sample Size

The study will be conducted over a period of 3 years. Currently, 10 countries with an approximate population base of 98 million have committed to participate in the study. We thus estimate there will be a total of approximately 50 000 patients' data collected.

Statistical Analysis

Data management will be carried out using the Clintrial application software version 4.2. All data analyses will be performed using SPSS version 11.0. Frequency tables and descriptive statistics with 95% confidence intervals for all outcome variables in section 5 will be presented. Location of cardiac arrests will be spot mapped using Geographic Information System (GIS) technology.

Univariate comparisons using t tests, chi-square tests or Fisher's exact test will be conducted as appropriate Logistic regression models will be developed for survival outcomes.

Potential Difficulties

One limitation is the great variation that exists in EMS systems and data collection across the Asia Pacific. It is thus crucial to establish common data definitions and a universal taxonomy for this study. This will allow valid comparison and aggregation of data across the different countries and EMS systems. The Executive Committee has set this as the first major task to be completed.

Another difficulty is that we need to account for various system and demographic factors in interpreting outcome differences for OHCA between study sites. Thus the importance of conducting a system-wide survey of participating sites to be able to describe country and EMS system specific population and structural factors. This will allow a baseline understanding for describing subsequent findings for OHCA and making valid comparisons of differences.

Finally, we can foresee the immense logistic challenges of conducting such a huge international study as this. We have established a model of collective participation, with each site taking responsibility for raising their own funding for the local portion of the study.

Nevertheless, the network will need leadership and investment to establish a centralized trial co-ordination center. This center will develop an easy to use, simple, internet-based Electronic Data Capture (EDC) system and will be responsible for training the various PIs and trial coordinators to use the system. We hope that NMRC will be able to support the establishment of the Singapore site and the trial co-ordination center through this proposal.

Future plans

We intend to follow up this study with prospective, multi-center clinical trials to improve survival from OHCA in the Asia-Pacific region. The initial survey and result from our proposed cohort study of the Pan-Asian Resuscitation Outcomes Network will be important to track trends and establish the baseline for subsequent clinical trials on the effectiveness of interventions related to our EMS systems.

For example, we intend to conduct a subsequent randomized trial by communities, comparing CPR alone and CPR with PAD in targeted communities. PAD will be augmented by web-based technology that will be able to send the nearest location of AEDs via cell phone to lay rescuers attending to a cardiac arrest.

EXPECTED BENEFITS

A Pan-Asian Resuscitation Outcomes Network will be an important foundation to implement and track planned improvements to EMS in the Asia-Pacific. It will provide user-friendly clinical research infrastructure, to conduct patient-oriented research (POR) (clinical, translational or services) in a high quality yet efficient manner. It will aid in planning for deployment of resources, interventions and ongoing efforts to improve EMS in the Asia-Pacific.

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Appendix 1: Timeline for establishing proposed OHCA EDC

Task	Milestone	Due Date
1	Create taxonomy and data dictionary	End Sep 2009
2	Design CRF	End Nov 2009
3	Set up operation committee and publication committee	End Jan 2010
4	Set up EDC and co-ordination meeting for members	Mid Mar 2010
5	- Create questionnaire - Survey of members	Mid Mar 2010
6	EDC training for member countries	Mid Jun 10
7	Launch EDC for OHCA study	June 2010 (ICEM 2010)
8	Manuscript completed for PAROS survey and submitted for publication	End 2010
9	Data collection completed for PAROS OHCA study and preparation for publication	June 2011

Task	Project Month/Year											
	Jul 09	Aug 09	Sep 09	Oct 09	Nov 09	Dec 09	Jan 10	Feb 10	Mar 10	Apr 10	May 10	Jun 10
1	█	█	█	█								
2				█	█	█						
3						█	█	█				
4							█	█	█	█		
5							█	█	█	█		
6										█	█	█
7												█
8												█
9												█

Task	Project Month/Year											
	Jul 10	Aug 10	Sep 10	Oct 10	Nov 10	Dec 10	Jan 11	Feb 11	Mar 11	Apr 11	May 11	Jun 11
8	█	█	█	█	█	█	█					
9	█	█	█	█	█	█	█	█	█	█	█	█

Appendix 3: Executive Committee of the Pan-Asian Resuscitation Outcomes (PAROS)

Clinical Research Network

Chair (2009): Sang Do Shin (Korea)

Vice Chair: Marcus Ong (Singapore)

Secretary: Jae Kwang Kim (Korea)

Member: Pairoj Khruengkarnchana (Thailand)

Member: William Woo (Hong Kong)

Member: Nik H Rahman (Malaysia)

Member: Matthew Ma (Taiwan)

Member: Hideharu Tanaka (Japan)

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List of potential network sites and principal investigators (2009)

Principal Investigator	Country	Sites	Population base
Sang Do Shin	Korea	6	20 million
Marcus Ong	Singapore	6	4 million
Matthew Huei-Ming Ma	Taiwan	2	10 million
William, Wing-Keung Woo	Hong Kong	5	10 million
Hideharu Tanaka	Japan	2	20 million
Pairoj Khruetakarnchana	Thailand	2	10 million
Nik H Rahman	Malaysia	2	5 million
Paul Middleton	Australia	3	10 million
Ridvan Atilla	Turkey	3	8 million
Ang Swee Hui	Brunei	1	400,000

List of Singapore sites and site principle investigators

NUH	Benjamin Leong (Deputy PI for Singapore)	benjamin_sh_leong@nuh.com.sg
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