Determining the Cost-Effectiveness of Strategies to Improve Survival from Out-Of-Hospital Cardiac Arrest in Singapore

Version 2.0

16 Nov 2010

CONTENTS

ABSTRACT

Background

Out of hospital cardiac arrest (OHCA) is a global health concern. Survival rates in Singapore are low (2%) compared to USA or Europe (up to 40%).

Design

This is a cost-effectiveness study based on prospective data from an international, multi-center cohort study of out-of-hospital cardiac arrest in Singapore and across the Asia-Pacific. The cost-effectiveness analysis for this study will be focused on Singapore's Emergency Medical Services (EMS) system.

Objectives

We aim to identify the most cost-effective strategy to improve survival from OHCA in Singapore. This will be based on a comparison of 5 competing (although not exclusive) strategies targeting major systemic and modifiable factors for OHCA survival.

The large sample size and international nature of the study provides a unique opportunity for analysis of preventable risk factors for OHCA and systemic predictors of survival. Identifying the relative incremental cost-effectiveness of modifiable factors for OHCA survival will allow prioritization and selection of 5 pre-identified competing interventional strategies (namely: increasing bystander cardio-pulmonary resuscitation, public access defibrillation, decreasing EMS response times, developing advanced EMS life support, specialized Cardiac Arrest Centers).

Methods

Data will be collected from emergency dispatch records, ambulance patient case notes, emergency department and in-hospital records. All completed data will then be collected and sent to the Study Co-ordination Center (Singapore) for data management using electronic data capture (EDC).

Our required sample size for the study is 13,447 OHCA patients and Singapore will contribute about 2,000 cases over 2 years. The relative effectiveness of the interventions associated with each of the 5 strategies will be determined. A cost analysis for the various strategies will be conducted to determine the incremental cost-effectiveness in Singapore for each strategy.

Eligibility

All OHCA patients presenting to EMS '995' or Emergency Departments during the study period as confirmed by the absence of pulse, unresponsiveness and apnea.

1. INTRODUCTION

OUT OF HOSPITAL CARDIAC ARREST IS AN IMPORTANT PUBLIC HEALTH CONCERN

Prehospital Emergency Care (PEC) 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, including OHCA, are anticipated to increase and place greater demands on PEC resources.

For example, of the approximately 16,000 deaths that occur in Singapore every year, about 23% will be from a cardiac cause[1] of which, some 30-40% will occur suddenly, outside of a hospital. That means we see >1000 deaths from OHCA a year in Singapore. The mechanism of death is usually a fatal arrhythmia, most often ventricular tachycardia or fibrillation[2]. Most of these patients die before ever reaching a hospital.

SINGAPORE HAS UNDERINVESTED IN PREHOSPITAL EMERGENCY CARE

With a population of 4.9 million, Singapore currently has a ratio of one emergency ambulance to 126,000 people[1]. This is far below international standards. The National Association of EMS Physicians (NAEMSP), USA, recommends that urban EMS systems should have approximately one ambulance for every 40,000 people with twice this ratio (i.e. 1:20,000) during peak call periods[3]. Emergency ambulance call volumes have been increasing by about 5% every year since 1998[4]. In particular, 109,459 emergency calls were received by the Singapore Civil Defence Force (SCDF) in 2007 – a 14% increase from 2006. Call volumes are expected to continue to rise with each year and increase the workload strain faced by emergency ambulance services.

Local performance has fallen behind international benchmarks. A study done in 2003 revealed that the local OHCA survival-to-hospital-discharge rate – an international benchmark for the effectiveness of a PEC system – was 2.0%[5]. This is lower than the median survival rate of 8.4% reported in a 2008 review of 10 PEC systems in

North America, and significantly below the best survival rate of 16.3% reported for Seattle, USA, in the same study[6]. The mean ambulance response times for cardiac arrest reported in Singapore is 10.2 minutes (90% <16.1 minutes). This is slower than the international benchmark ambulance response time of 90% <8 mins[7, 8].

Early initiation of treatment has an important effect on outcomes and survival[9], and this has to begin before a patient even arrives at a hospital. For example, in OHCA, every minute this is left unattended, chances of survival will decrease by 7-10%[10]. The question for Asian countries like Singapore is, where do we begin? How can we improve prehospital emergency care in an evidence-based manner, with the limited resources available? What intervention strategies will give the most benefit for investment?

MODIFIABLE FACTORS FOR SURVIVAL

We hypothesize that there are several major modifiable factors for OHCA survival. However most of our understanding regarding these possible factors comes from relatively small studies in Western populations. We know that early initiation of treatment has an important effect on outcomes and survival[11]. This is illustrated by the 'chain of survival' concept[9] for cardiac arrest patients. This concept states that early initiation of the four 'links' in the chain of survival, will all improve survival in OHCA. The links are 'early access' activating the Emergency Medical Services (EMS) system by calling medical dispatch or 995, 'early 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%[10]. There is currently good research that indicates survival can be improved with shorter ambulance response times[7, 12-14], early CPR[11, 15] and early defibrillation[8, 16-18].

From a system point of view, North American studies have identified several modifiable factors that predict survival from OHCA[16, 19]. These include bystander CPR rates, defibrillation, EMS response time and post-resuscitation care among others. Our study will look at the impact of such system factors on OHCA survival, and the components in our national EMS system that might be amenable for possible intervention to improve survival.

What is unclear is the relative importance of these factors compared with each other in an Asian setting. We hypothesize that there are differences in the population demographics, underlying disease burdens and the incidence of primary ventricular fibrillation in Asian populations compared to Western ones. The likely priority of interventional strategies for OHCA in Asia will also be different from Western countries, where EMS systems are relatively more developed and high bystander CPR rates, public access defibrillation and advanced life support EMS may already be entrenched. For example, a primary strategy to increase bystander CPR might have a much greater impact in Singapore (baseline bystander CPR rate <20%), compared to Seattle, Washington (40-50%). The cost environment for interventions in EMS will also be different in Singapore compared to the West.

Based on our extensive literature review, we have identified 5 potential strategies for improving survival rates for OHCA in Singapore. Identifying the incremental cost-effectiveness of modifiable factors for OHCA survival will allow prioritization and selection of these competing (although not exclusive) interventional strategies, namely:

1. Widespread community based and systemic efforts to increase bystander cardiopulmonary resuscitation

In an Ontario, Canada study, the Ontario Prehospital Advanced Life Support (OPALS) investigators concluded that bystander CPR was the most important modifiable factor for OHCA survival, odds ratio 2.98 (95% confidence interval 2.07 to 4.29)[19]. However, we also note that at the time of this study, it was conducted in the setting of Basic Life Support (BLS) EMS system. In Singapore, the current bystander CPR rate is 20%[5]. This is much lower than the rate of 31% reported across the Resuscitation Outcomes Consortium (ROC) sites[6], and up to 55% reported in other studies[20, 21].

A strategy to improve bystander CPR rates would require a concerted public health effort to educate and train the population to perform CPR. Quality of CPR is also an important issue[22], which requires maintenance of skill by continuous recertification and possible dissemination of CPR feedback technology[23]. It should be noted that

such a strategy would be labour intensive, and require a long term approach to see fruit. It might also prove to be a relatively costly strategy, considering the large number of people that would need to be trained in order to see any improvement in bystander CPR rates[24].

2. Investing in public access defibrillation

In a prospective, community-based, multicenter clinical trial, community units were randomly assigned to a structured and monitored emergency-response system involving lay volunteers trained in CPR alone or in CPR and the use of automated external defibrillators (AEDs)[25]. They found increased survivors in the AED group, relative risk (survival) 2.0 (95% confidence interval 1.07 to 3.77). This has led to advocacy for Public Access Defibrillation (PAD), with widespread dissemination of AEDs in the community. PAD is currently very rare in Singapore.

A strategy involving PAD will be relatively more expensive to implement, as the cost of AEDs are currently at least USD$1,000 a piece[26]. However it may promise to give additional survivors by introducing earlier defibrillation at the scene of a collapse. The question still remains, what is the additional benefit of PAD in the Asian setting? Questions also remain about how many devices need to be deployed, where should they be sited and what community response systems need to be in place to ensure that these devices are appropriately used[27] ?

3. Having a Basic Life Support (BLS) EMS system, but investing in reducing response times

Singapore's current EMS system is primarily a BLS model, with ambulance crews able to only perform CPR and defibrillation. Yet response times are relatively long, with a mean (SD) EMS response time of 10.2 (4.3) minutes[5]. This is well above the National Association of EMS Physician's (NAEMSP) recommendation of 90% <8 minutes, or studies that suggest response times for OHCA should be <4 minutes[14].

The OPALS study found that a strategy to reduce response times and provide early defibrillation was able to improve survival to hospital discharge from 3.9% to 5.2 % (p = 0.03)[28]. The 33% relative increase in survival represented an additional 1 life per 120,000 residents saved each year in the study communities.

A strategy to improve response times in Singapore would involve optimizing the 995 dispatch system, deploying appropriate numbers of ambulances, using advanced ambulance deployment algorithms[29] and the use of motorcycle or fire based first responders[30].

4. Developing advanced life support (ALS) EMS system

ALS EMS is the standard of care for many North American and European communities. ALS includes advanced airway management such as endotracheal intubation as well as use of intravenous drugs. Yet there is relatively little evidence for the effectiveness of ALS EMS in OHCA. There is evidence that amiodarone is helpful in ventricular fibrillation[31, 32], however the benefit of endotracheal intubation[33] and epinephrine (adrenaline) seems unclear[34, 35]. In addition, the OPALS study found that the addition of ALS did not improve survival from BLS with rapid defibrillation[36].

A strategy involving ALS EMS will involve training, upgrading and equipping paramedics to perform advanced cardiac life support in the field. However questions remain regarding which elements of ALS (e.g. endotracheal intubation, intravenous drugs?) are truly effective? Also will advanced skills like endotracheal intubation be easy to maintain and what about complication rates?

5. Investing in hospital-based post resuscitation care (Cardiac Arrest Centers)

Recently, advances in post resuscitation care, has shown promise to improve survival from OHCA. Most prominently, two randomized controlled trials have shown hypothermia after cardiac arrest is able to improve survival with intact neurological function[37, 38]. This has led to a movement towards regionalization of OHCA care and calls for the establishment of cardiac arrest centers[39].

A strategy involving optimized post-resuscitation care would involve establishing designated cardiac arrest centers, where hypothermia and other modalities such as Extracoporeal Membrane Oxygenation (ECMO) are available. However this requires diversion of ambulances transporting such patients, and considerable cost and effort to establish such centers of excellence.

SELECTION OF INTERVENTION STRATEGIES

In an ideal world, with no funding constraints, one could argue that you could pursue all these strategies simultaneously. In practice, resources are limited and policy decisions have to be made regarding priority of investment in a particular strategy. Which strategy or combination of strategies, will give the maximum survival benefit for the most cost-effective investment? This is a very real policy question that is being asked at the Ministry of Health (MOH), Singapore, and is referred to in a recent 5 year MOH blueprint for Prehospital Emergency Care.

LACK OF EVIDENCE FROM RANDOMISED CONTROLLED TRIALS

There is currently little evidence to guide us on this question from randomized controlled trials. Ethically and logistically, it would be almost impossible to conduct large scale clinical trials comparing these competing strategies. Furthermore, many EMS practices are rooted in structural and systemic issues, and would require massive efforts to effect change, even on a trial or pilot basis. This makes traditional clinical trials-type approaches to answer the question impractical or unworkable. Singapore is also too small to conduct the large sample cohort type studies need to answer this type of question. It would take an impractically long time in order to recruit the kind of numbers needed for such a study.

Hence, a large international cohort study, taking advantage of the inherent variations in Asia-Pacific EMS systems provides a unique opportunity for analysis of the modifiable risk factors and systemic predictors of survival for OHCA. For example, we will be able to analyse the univariate and multivariate effect of bystander CPR on survival from OHCA across all our Asia-Pacific study sites. This will enable us to derive the relative importance of bystander CPR (Strategy 1) and the possible effectiveness of a strategy to increase bystander CPR. Similarly, the study will also provide data on the effect of public access defibrillation (Strategy 2), response times (Strategy 3), advanced life support (advanced airway management like endotracheal intubation or advanced airway devices, intravenous drugs – Strategy 4) and specialized post-resuscitation care (hypothermia, ECMO - Strategy 5).

An analysis of the local costs involved in implementing any potential strategy will also be important in assessing incremental cost-effectiveness. This will enable us to answer the policy question facing us in the most evidence-based manner available.

TAKING ADVANTAGE OF VARIATION IN OHCA MANAGEMENT AND OUTCOMES

Worldwide, there is wide regional variation in OHCA management and outcomes[6]. 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 America[6]. From this and other retrospective reviews of OHCA across different EMS systems[40], we know that startling variations exist in the treatment 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%) [41-44]. We believe that such variations exist in the Asia Pacific as well; both within various EMS systems in countries and between countries (see Appendix 1).

The large sample size and international nature of our proposed study will allow analysis of the influence of EMS characteristics, bystander CPR, EMS response times, prehospital defibrillation and treatment on OHCA outcomes. Among our different sites, there will be considerable variation in the current strategies and emphasis of their EMS system. For example, Japan has a high penetration of PADs and bystander CPR but they run a mostly BLS EMS. Australia has mostly ALS paramedics on ambulances. Korea and Taiwan have embarked on hypothermia after cardiac arrest as ECMO technology, but run BLS EMS systems. By adopting a common taxonomy and standardizing outcomes reporting across the network, we will be able to determine the relative importance of these system factors for OHCA survival. We will be able to generate odds ratios and confidence intervals for these modifiable factors on survival. These effectiveness results will be used for the cost-effectiveness analysis phase of our study.

Variations in the outcomes of OHCA might also be due to fixed underlying population differences (age, ethnicity) as well as predisposing factors and chronic disease

burdens. These will need to be adjusted for in a multivariate regression analysis to discern the effect of modifiable factors for survival.

THE IMPORTANCE OF DENOMINATORS

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 approach[6]. A population based assessment of the true burden of out-of-hospital cardiac arrest and potential characteristics that improve survival would be key for this study.

A related 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[45, 46]. 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.

The International Liaison Committee on Resuscitation (ILCOR) suggests that OHCA should be a reportable health outcome[47] and advocates a standardized reporting in the 'Utstein style'[48]. The Utstein style is a standardised reporting format for OHCA that has been adopted by ILCOR.

COMPARING EMS OUTCOMES

Before comparing outcomes, we need to account for the vast variation that exists in EMS systems internationally. This has a direct impact on the variation of OHCA outcomes seen in various studies[40-44]. Describing the spectrum of EMS services across our study sites will give insights into subsequent comparison of outcomes, and might highlight best practices[49]. 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 arrests[50] (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'.

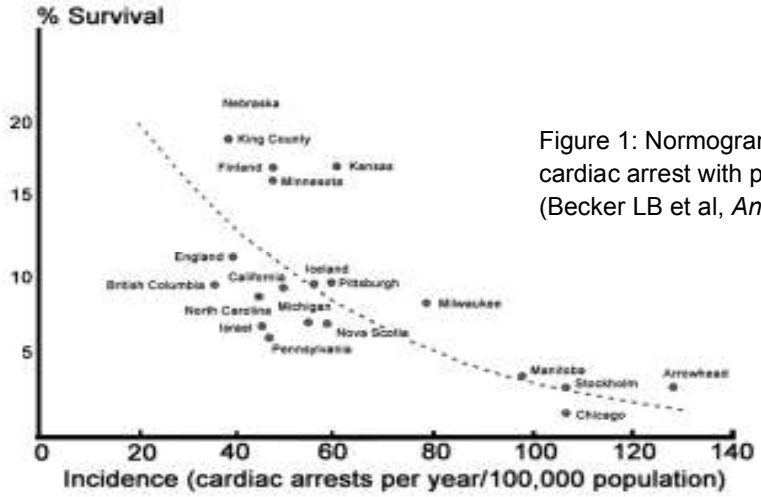

Figure 1: Normogram relating population incidence of cardiac arrest with predicted survival
(Becker LB et al, *Ann Emerg Med* Jan 1993; 22(1): 86-91)

ROLE OF PRIMARY VENTRICULAR ARRHYTHMIAS

Another reason why we believe this study will be important is there are 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. This means that strategies for OHCA derived from purely Western studies, might not be totally applicable in an Asian setting.

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% [51-53] and the commonest presenting rhythm is asystole. This is compared to 23-56% [6, 44] 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? 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? 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.

PAN-ASIAN RESUSCITATION OUTCOMES NETWORK

There is an urgent need for good quality research and 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 OHCA[5] which may serve as a model for a Pan-Asian Resuscitation Outcomes (PAROS) network. Another example of a clinical research network (CRN) focused on Resuscitation is the Resuscitation Outcomes Consortium of North America[6, 45, 54] and the Cardiac Arrest Registry to Enhance Survival[55].

We believe that establishing a resuscitation outcomes 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 and other prehospital emergency conditions. Such efforts will require multi-pronged strategies targeting the community, EMS and the hospitals.

By riding on the PAROS network, we will also be able to answer the important health policy questions we have posed relating to our local EMS system.

VALUE TO SINGAPORE

This study can help to answer key policy questions that will assist in the formulation of a National Prehospital Emergency Care Blueprint. This is a major effort currently being undertaken by the Hospital Services Division of the Ministry of Health. Results from such research can help guide such policy from the basis of evidence.

Socially, we see the benefit of such research in improving survival rates for OHCA patients in Singapore. The research effort will also raise EMS treatment capability in Singapore and the research infrastructure.

We see that this study can become a platform for investigator and pharmaceutical or medical device company initiated clinical trials for OHCA in Asia. This will cement Singapore's efforts to become a leading center for conducting such international research.

As for the scientific value, we see this study helping to develop local experience in establishing a multi-site platform for clinical trials and networks. It can also help promote the scientific careers of Singaporeans and establish their credentials in conducting international studies.

This study will be a continuation and expansion of the work of the CARE study in study. 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 (now known as Singapore Clinical Research Institute). CARE phase I found survival from out-of-hospital cardiac arrest in Singapore to be 2.0%[5]. Mean (SD) EMS response time was 10.2 (4.3) minutes. Mean (SD) time from call to defibrillation was 16.7 (7.2) minutes. This study was launched in 1999 and was supported by grants from NMRC and SingHealth. To date, it has generated more than 16 international and local publications and has had a major impact on health policy in Singapore. It has also generated interest in the international EMS community and is often referenced as a model for EMS research in Asia.

In subsequent phases, the group has looked at the effect of various interventions in cardiac arrest[34, 56, 57], cardiac arrest in specific situations[58, 59] and community attitudes towards cardiac arrest[60-62]. Recently, we completed a study describing the geographic epidemiology of prehospital cardiac arrest in Singapore[27].

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. So far, a total of 10 countries across the Asia-Pacific have committed to this study (see Appendix 2). Together, the study sites represent a population base of 98 million.

We have also collaborated with the Cardiac Arrest Registry to Enhance Survival (CARES), funded by Centers for Disease Control (CDC), Atlanta, USA[55] to come up with a unified taxonomy and data dictionary for the study. We will standardise all

definitions across the PAROS network by adopting a consensual common taxonomy and data collection methodology. This will allow valid comparison of population based incidence and outcomes across network sites and create an opportunity for comparison of data across the globe.

In addition, the CARES-CDC has promised technical support for the study, including assistance in setting up a server based in Singapore running the electronic data capture (EDC) platform.

Singapore Clinical Research Institute (SCRI) will act as the data co-ordination center for PAROS. In addition, the Duke-NUS Health Services Research program will support the economic analysis for this study.

2. OBJECTIVE AND HYPOTHESIS

We aim to identify the most cost-effective strategy to improve survival from OHCA in Singapore. This will be based on a comparison of 5 pre-identified competing (although not exclusive) strategies targeting major systemic and modifiable factors for OHCA survival.

We hypothesize that there are several major modifiable factors for OHCA survival. However most of our understanding regarding these possible factors comes from relatively small studies in Western populations. What is unclear is the relative importance of these factors compared with each other in any Asian setting. The likely priority of interventional strategies for OHCA in Singapore will also be different from Western countries, where EMS systems are relatively more developed and high bystander CPR rates, public access defibrillation and advanced life support EMS may already be entrenched.

Based on an extensive literature review, we have identified 5 potential strategies for improving survival rates for OHCA in Singapore, namely:

1. Widespread community based and systemic efforts to increase bystander cardio-pulmonary resuscitation

2. Investing in public access defibrillation
3. Having a basic life support EMS system, but investing in reducing response times
4. Developing advanced life support EMS system
5. Investing in hospital-based post resuscitation care (e.g. Cardiac Arrest Centers)

In an ideal world, with no funding constraints, one could argue that you could pursue all these strategies simultaneously. In practice, resources are limited and policy decisions have to be made regarding priority of investment in a particular strategy. Which strategy or combination of strategies, will give the maximum survival benefit for the most cost effective investment? This is a very real policy question that is being asked at the Ministry of Health, Singapore, and is referred to in a recent 5 year MOH blueprint for Prehospital Emergency Care. Identifying the incremental cost-effectiveness of these strategies for OHCA survival will allow prioritization and selection among these interventional strategies

This cost-effectiveness study will be based on prospective data from an international, multi-center cohort study of out-of-hospital cardiac arrest in Singapore and across the Asia-Pacific. The cost-effectiveness analysis will be focused on Singapore's EMS system.

We aim to identify the relative importance/effect of major systemic, modifiable factors (and thus their related interventional strategies) for OHCA survival in Singapore and the Asia Pacific. The large sample size and international nature of the study provides a unique opportunity for analysis of the preventable risk factors and systemic predictors of survival for OHCA. This study will be the basis and prelude to a major interventional trial to improve survival rates for OHCA in Singapore and across Asia. We aim to improve survival rates for OHCA in Singapore, and also establish a leading role for Singapore in the international scientific effort.

This national Cardiac Arrest Resuscitation Outcomes Study (Singapore) will be part of a PAROS comparative study. The PAROS Clinical Research Network (CRN) was established to provide user-friendly clinical research infrastructure, to conduct

patient-oriented clinical, translational and services research in a high quality yet cost-efficient manner. Singapore will be the trial coordinating center for the PAROS CRN and this will secure a leading role for Singapore in an international collaborative scientific effort. In addition, the PAROS CRN is in turn linked to CARES.[55]

3. METHODS

3.1 STUDY DESIGN

This is a cost-effectiveness study based on retrospective and prospective data from an international, multi-center cohort study of out-of-hospital cardiac arrest in Singapore and across the Asia-Pacific. Retrospective data collection period for Singapore sites will start from April 2010. The cost-effectiveness analysis for this study will be focused on Singapore's EMS system.

3.2 SETTING

Singapore is a city-state with a land area of 710.2 square kilometers and a population of 4.9 million. Singapore's EMS system is run by the SCDF, which operates the national 995 (universal access number) emergency telephone service. '995' is a universal, centralized, enhanced dispatching system, utilising computer aided dispatch, medical dispatch protocols, global positioning satellite automatic vehicle locating systems and road traffic monitoring systems. Currently SCDF operates 46 ambulances based in 15 fire stations and 16 satellite stations. They utilise a fixed deployment system operating out of these geographically static stations and it is primarily a single tier system.

Since 1996, ambulances in Singapore have been manned by specifically trained paramedics (roughly equivalent to North American EMT-Intermediate), replacing the nurses that previously served as ambulance officers. The paramedics undergo an 18-month training including theory, hospital and ambulance attachments. They are able to provide basic life support and defibrillation with AED. They are able to give symptom relief medication like salbutamol, nitroglycerin, diazepam, aspirin,

intravenous adrenaline (epinephrine), dextrose and saline infusions. They also perform laryngeal mask airway insertion in cardiac arrest.

3.3 INCLUSION CRITERIA

- All OHCA conveyed by EMS '995' or presented at Emergency Departments during the study period as confirmed by the absence of pulse, unresponsiveness and apnea.

3.4 EXCLUSION CRITERIA

- Patients who are immediately pronounced dead, and for whom resuscitation is not attempted, including decapitation, rigor mortis and dependent lividity.

3.5 OUTCOMES

Primary outcome:

- Survival to hospital discharge or survival to 30 days post cardiac arrest,

Secondary outcomes:

- Return of spontaneous circulation
- Survival to hospital admission
- Neurological status on hospital discharge or on 30th day post cardiac arrest, if not discharged
- Quality of life assessment for survivors

3.6 VARIABLES MEASURED

Definitions will follow Utstein recommendations[63] as well as conform to a unified taxonomy established by the PAROS network.

Variables collected will include:

- bystander CPR (Strategy 1)
- public access defibrillation (Strategy 2)
- response times (Strategy 3)

- advanced life support (advanced airway management like endotracheal intubation or advanced airway devices, intravenous drugs – Strategy 4)
- specialized post-resuscitation care (hypothermia, ECMO- strategy 5)
- Glasgow-Pittsburg Outcome Categories (Cerebral Performance Category and Overall Performance Category) (see Appendix 3)
- European quality of life - 5 dimensions (EQ-5D) Health Dimensions and Visual Analog Scale

We will also collect data on the geographical location of OHCA which will be mapped using ArcView GIS (ESRI).

System variables will also be collected as stated in data collection form.

3.7 LOGISTICS

EMS data will be collected from both from '995' dispatch records, as well as ambulance patient case notes. EMS timings will be automatically recorded by the computerised central dispatch system.

Hospital data will be collected from the Emergency Departments, Intensive Care Units and wards. Inpatient discharge summaries and death certificate information will also be assessed. For survivors, quality of life will be assessed with the European quality of life-5 dimensions (EQ-5D). EQ-5D is a standardized instrument used in measuring quality of life. It provides a descriptive profile of patient's health status in 5 dimensions.

Data entry will be done using EDC. The EDC is an online, data registry system that will be set up with assistance from SCRI, CARES-CDC Atlanta USA, Duke-NUS Graduate Medical School and Singapore General Hospital. Data management will be done by SCRI.

3.8 INFORMED CONSENT ISSUES

We are applying for waiver of consent as we will be only reviewing documents for all the enrolled cardiac arrest cases. There will be no patient or family interaction or intervention involved. All patients' identifiers will be removed from the dataset to protect patients' privacy and confidentiality.

However, we will obtain informed consent from patients who survived to hospital discharge to assess their quality of life using EQ-5D. Only patients with Glasgow Coma Scale: cerebral and overall performance scoring of 2 and below will be selected for the assessment. No patient's indentifers will be recorded during the EQ-5D asssessment to protect their prvacy and confidentiality.

3.9 STATISTICAL CONSIDERATIONS

Sample size

The primary aim of the effectiveness portion of the study is to identify the factors (and thus the related interventional strategies) associated with better survival outcome among OHCA patients in the Singapore. To compute the sample size, we looked at each potential risk factor and identified the one (community size <30,000) which would require the largest sample size to assess. A previous study from Canada had reported that the probability of exposure (community size <30,000) among controls (non-survivors) was 0.05[19]. To detect an odds ratio for disease in exposed subjects relative to unexposed subjects of 1.4, we will need to study 13,447 OHCA patients to be able to reject the null hypothesis (using an uncorrected chi-squared statistic) that the odds ratio equals to 1, with type I error of 0.05 and power of 90%[64].

In addition, applying the approach recommended by Peduzzi et al, assuming we have 20 potential risk factors to evaluate, the minimum sample size required would be given by n =10 X (the number of risk factors)/(the smallest proportion of positive or negative cases in the population) = 7,407[65]. Hence 13,447 OHCA patients will be sufficient to also meet these criteria.

We expect that over the period of the study, Singapore will contribute about 2,000 cases over 2 years. This is based on the experience from the CARE 1 study regarding OHCA occurrence in Singapore[5].

Statistical Analysis

Descriptive statistics including frequencies, means and their standard deviation (SD), medians and quartiles will be obtained for the socio demographic and other independent variables as appropriate.

For independent variables with more than two categories, dummy variables will be created. The categories of variables having sparse data will be grouped together in biologically meaningful ways. The category with minimum level of potential risk (hazard) of survival will be taken as the reference group for each risk (prognostic) factor. Univariate analysis will be carried out and odds ratios (ORs) and corresponding 95% confidence intervals (CI) will be computed to estimate the association between the dependent variable (survival status) and each factor.

The independent variables associated with survival status at 0.25 significance level in the univariate analysis or those with biological importance will be further analyzed through multivariate logistic regression to arrive at the most parsimonious, biologically meaningful model. Variables found to be not statistically significant ($p > 0.05$) from the multivariate analysis, or biologically not important, will be subsequently removed from the model. The overall significance of the independent variables in the model will be assessed by the Likelihood ratio test. Confounding will be assessed by ≥10% change in the estimated coefficient for the particular variable. After developing the main effect model, to uncover any multicollinearity, the association among independent variables will be assessed by using the appropriate test and plausible interactions between the independent variables will also be assessed. The Pearson's Chi-square test will be applied to check for the goodness-of-fit of the final model.

3.10 COLLECTION OF COSTING DATA FOR SINGAPORE

We will conduct a detailed costing estimate of each element of the five strategies, to derive the potential cost of implementing a particular strategy. Costing data will be obtained from the Ministry of Health, SCDF, National Resuscitation Council (NRC), hospitals and other collaborating bodies for this study.

Strategy 1

In order to achieve a bystander CPR rate of 50% in Singapore, the NRC has estimated that it will require the training of an additional 4000 CPR instructors, and conducting an additional 100,000 CPR courses per year over the next 5 years. Costing estimates will be obtained from NRC regarding the cost of both CPR and instructor courses. Costs will also be obtained from the Health Promotion Board (HPB) regarding the cost of a public campaign to encourage bystander CPR.

Strategy 2

In order to achieve a mean time-to defibrillation time of 4 minutes for OHCA victims in Singapore, we estimate it will require a public access defibrillation penetration of at least 1 AED per 100 persons. Training of laypersons to use an AED will be pegged on to 'CPR+AED' courses run according to NRC requirements. Costing estimates will be obtained from NRC as per strategy 1. In additional, costs for a public campaign by HPB will also be similar to strategy 1. A deployment strategy for AEDs will be derived from an analysis of the geospatial occurrence of OHCA obtained from this study.

Strategy 3

In order to reduce response times for the highest priority ambulances calls to 90% <9 minutes, a double strategy of increasing ambulance numbers and smarter deployment using Systems Status Management (SSM) will be considered. We estimate it will require an ambulance to population ratio of 1:40,000, translating to an additional 46 ambulances compared to current levels. Costing data will be obtained from SCDF regarding the annualized cost of each additional ambulance needed, as well as the costs of training the additional 184 paramedics needed, as well as annual manpower costs. Costs will also be estimated for implementing a SSM plan. A

deployment strategy for ambulances will be partially derived from an analysis of the geospatial occurrence of ambulance calls obtained from this study.

Strategy 4

In order to implement a two tiered, ALS ambulance response, we will base estimates on adding additional ALS ambulances to existing BLS ones, using the ratios given is strategy 3. Thus we will obtain annualized costing estimates for an additional 46 ALS ambulances from the SCDF. The costs for training an additional 184 ALS paramedics will be obtained from SCDF and Nanyang Polytechnic/Justice Institute of British Columbia.

Strategy 5

We estimate strategy 5 will require the establishment of at least 3 cardiac arrest centers in Singapore. Costing estimates will be obtained from the Singapore General Hospital on setting up, and maintaining a 24/7 cardiac arrest center, capable of emergency percutaneous coronary intervention, hypothermia after cardiac arrest, extra-corporeal membrane oxygenation and other advanced post resuscitation care.

3.11 COST-EFFECTIVENESS ANALYSIS

We will conduct a cost-effectiveness analysis from a societal perspective based on the cost and effectiveness data derived for the 5 strategies. To conduct the analyses, we will obtain the incremental cost-effectiveness ratio (ICER) for each of the 5 strategies, with effectiveness being defined in terms of Quality Adjusted Life Years (QALYs) saved as a result of each intervention.

Our cost-effectiveness analysis follows the approach described in the literature[66, 67] and in several previous studies successfully conducted for EMS system research in North American settings[24, 26, 68]. Below we provide a hypothetical example to illustrate our method (Table 1&2, Figure 2). First, costs and effectiveness measures are tabulated for each strategy in order of increasing costs (Table 1). We then check for whether any intervention is dominated in either a strict sense (higher cost and lower effectiveness than a preceding option) or in an extended sense (higher ICER than the subsequent option)[67]. In our hypothetical example, no intervention is

dominated in a strict sense because all costlier interventions are also more effective. However, Strategy 1 is dominated in an extended sense because the ICER of Strategy 1 is greater than the ICER of Strategy 2. Therefore, we eliminate Strategy 1 for further consideration and re-estimate the ICERs for the remaining strategies. No other intervention was found to be dominated in an extended sense.

Strategies	Average Cost per person	Average Effectiveness (QALYs)	Incremental Cost (∆C, $)	Incremental Effectiveness (∆E, QALYs)	Incremental C-E Ratio (∆C/∆E)
Status quo	$3,000	0.15	-	-	-
1. ↑ Bystander CPR	$7,000	0.25	$4,000	0.10	$40,000
2. ↑ PAD with 1	$8,000	0.35	$1,000	0.10	$10,000
3. BLS with ↓ response time	$12,500	0.45	$4,500	0.10	$45,000
4. ALS	$25,000	0.55	$12,500	0.10	$125,000
5. Post-resuscitation center	$40,000	0.60	$15,000	0.05	$300,000

Table 1. Preliminary Tabulation for Cost-Effectiveness Analysis

After removing Strategy 1, we generate new ICERs for the non-dominated strategies (Table 2).

Strategies	Average Cost per person	Average Effectiveness (QALYs)	Incremental Cost (∆C, $)	Incremental Effectiveness (∆E, QALYs)	Incremental C-E Ratio (∆C/∆E)
Status quo	$3,000	0.15	-	-	-
2. ↑ PAD with 1	$8,000	0.35	$5,000	0.20	$25,000
3. BLS with ↓	$12,500	0.45	$4,500	0.10	$45,000
4. ALS	$25,000	0.55	$12,500	0.10	$125,000
5. Post-resuscitation center	$40,000	0.60	$15,000	0.05	$300,000

Table 2. Full Tabulation for Cost-Effectiveness Analysis after Excluding Dominated Strategy 1

This iterative process can be illustrated graphically (Figure 2). The slope of the line segments represents the ICER for each strategy. Strategy 1 is removed because, for its cost of $7,000, one could obtain greater QALYs by offering a mix of the status quo and Strategy 2.

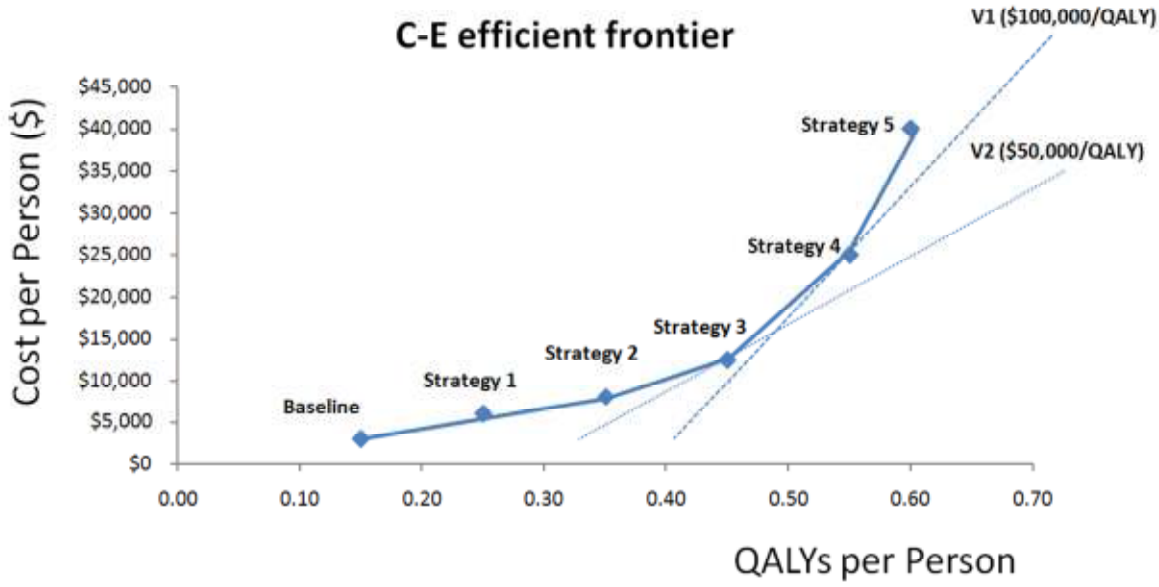

Figure 2. Efficient Frontier in Cost-Effectiveness Analysis

Figure 2 also provides an important insight as to how to choose the most cost-effective strategy. For the decision maker, it is important to take into account a budget constraint on how much the society is willing to pay for a unit gain in QALYs[69]. This can be illustrated using lines V1 and V2. If the society were willing to pay a maximum of $50,000 for a unit gain in QALYs (in the case of V2), then Strategy 3 would be the most preferred option. In the case of V1 ($100,000/QALY), where the society has a higher willingness-to-pay (or opportunity cost) for one unit of QALY, as shown by its steeper slope than that of V1, Strategy 4 would be the most preferred option. Also, it can be determined what will be the range of values of V for which a given intervention will be chosen by comparing the slope of the budget line against the slope of each of the line segments forming the efficient frontier.

Finally, we will examine whether the cost-effectiveness analysis results are affected by changes in model parameters such as key assumptions made in the cost analysis.

We will perform one-way (and n-way) sensitivity analyses in which we examine the effect of changing one (or n) of the model parameters, holding all other parameters constant. Our cost-effectiveness analysis results will also be presented in the form of cost-effectiveness acceptability curves, which will show the probability that each strategy is cost-effective, for a range of monetary values that a decision-maker might be willing to pay for a unit change in QALYs.

3.12 POTENTIAL DIFFICULTIES

One potential difficulty is that data collection methods currently vary 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.

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.

4. TIMELINE

Launch of the electronic data capture for the study and data collection begins	April 2010
Data collection completed	March 2012
Data analysis and preparation for publication	September 2012

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Appendix 1

Characteristics of PAROS Site Countries

Country	Bystander CPR (%)	PAD	EMS Response Times (minutes)	ALS	Post Resuscitation Care Hypothermia/ ECMO
Singapore	20.6[5]	+	10.4[5]	+	+
Korea	1.5[70]	+	6[70]	+	++
Taiwan	4.2[71]	+	4.89[72]	++	++
Hong Kong	15.6[53]	+	6[73]	+	-
Japan	36[74]	+++	5[75]	++	+++
Thailand	-	-	12.6[76]	+	-
Malaysia	8.7[77]	-	25.6[78]	-	-
Australia	36.7[79]	++	8[79]	+++	+++
Turkey	1.7[80]	-	11.3[81]	+	-
Brunei	-	-	30[82]	-	-

Abbreviations:
PAD – Public Access Defibrillator
ALS – Advanced Life Support
ECMO – Extra-Corporeal Membrane Oxygenation
+ - rarely implemented
++ - moderate implementation
+++ - widespread implementation

Appendix 2

Number of Participating Sites

Country	Sites	Population base
Korea	6	20 million
Singapore	6	4 million
Taiwan	2	10 million
Hong Kong	5	10 million
Japan	2	20 million
Thailand	2	10 million
Malaysia	2	5 million
Australia	3	10 million
Turkey	3	8 million
Brunei	1	400,000

Appendix 3

Glasgow-Pittsburg Outcome Categories

Score	Cerebral Categories	Score	Overall Performance Categories
1	Good cerebral performance. Conscious. Alert, able to work and lead a normal life. May have minor psychological or neurological deficits (mild dysphasia, non-incapacitating hemiparesis, or minor cranial nerve abnormalities).	1	Good overall performance. Healthy, alert, capable of normal life. Good cerebral performance (CPC 1) plus no or only mild functional disability from noncerebral organ system abnormalities.
2	Moderate cerebral disability. Conscious. Sufficient cerebral function for part-time work in sheltered environment or independent activities of daily life (dressing, travelling by public transportation, and preparing food). May have hemiplegia, seizures, ataxia, dysarthria, or permanent memory or mental changes.	2	Moderate overall disability. Conscious. Moderate cerebral disability alone (CPC 2) or moderate disability from noncerebral system dysfunction alone or both. Performs independent activities of daily life (dressing, travelling, and food preparation). May be able to work part-time in sheltered environment but disabled for competitive work.
3	Severe cerebral disability. Conscious. Dependent on others for daily support because of impaired brain function (in an institution or at home with exceptional family effort). At least limited cognition. Includes a wide range of cerebral abnormalities from ambulatory with severe memory disturbance or dementia precluding independent existence to paralytic and able to communicate only with eyes, as in the locked-in syndrome.	3	Severe overall disability. Conscious. Severe cerebral disability alone (CPC 3) or severe disability from non-cerebral organ system dysfunction alone or both. Dependent on others for daily support.
4	Coma, vegetative state. Not conscious. Unaware of surroundings, no cognition. No verbal or psychological interactions with environment.	4	Same as CPC 4.
5	Death. Certified brain dead or dead by traditional criteria.	5	Same as CPC 5.

Appendix 4

Patient Information Sheet and Informed Consent Form

SingHealth

PARTICIPANT INFORMATION SHEET

You are being invited to participate in a research study.

Before you take part in this research study, the study must be explained to you and you must be given the chance to ask questions. Please read carefully the information provided here. If you agree to participate, please sign the informed consent form. You will be given a copy of this document to take home with you.

STUDY INFORMATION

Protocol Title:

Determining The Cost-Effectiveness Of Strategies To Improve Survival From Out-Of-Hospital Cardiac Arrest In Singapore

Principal Investigator(s):

A/Prof Marcus Ong Eng Hock
Department of Emergency Medicine, Singapore General Hospital
Tel: 6321 3590

PURPOSE OF THE RESEARCH STUDY

You are being invited to participate in a research study of out-of-hospital cardiac arrest. We hope to collect descriptive profile of patient's health status after surviving an out-of-hospital cardiac arrest event. You were selected as a possible subject in this study because you have survived an out-of-hospital cardiac arrest event.

This study will recruit about 2,000 subjects from *SGH, NUHS, TTSH, CGH, KTPH, KKH and JGH* over a period of 2 (two) years from 1 June 2010 to 31 May 2012. However only about 100 subjects will be involved in this assessment for the study.

STUDY PROCEDURES

If you agree to take part in this study, you will be asked to complete a quality of life survey which consists of six (6) simple questions.

WITHDRAWAL FROM STUDY

You are free to withdraw your consent and discontinue your participation at any time without prejudice to you or effect on your medical care. If you decide to stop taking part in this study, you should tell the Principal Investigator.

If you withdraw from the study, your quality of life assessment will not be included in the research study.

POSSIBLE RISKS, DISCOMFORTS AND INCONVENIENCES

There are no potential risks, discomforts and inconveniences in this research, as it does not

involve any intervention or device. It only involves completing a quality of life survey which consists of six (6) simple questions.

POTENTIAL BENEFITS

There is no assurance you will benefit from this study. However, your participation may contribute to the medical knowledge for improvement in survival and management of out-of-hospital cardiac arrest.

SUBJECT'S RIGHTS

Your participation in this study is entirely voluntary. Your questions will be answered clearly and to your satisfaction.

You have the right to refuse your quality of life assessment to be studied now or saved for future study. By signing and participating in the study, you do not waive any of your legal rights to revoke your consent and withdraw from the study at any time.

CONFIDENTIALITY OF STUDY AND MEDICAL RECORDS

Information collected for this study will be kept confidential. Your records, to the extent of the applicable laws and regulations, will not be made publicly available. Only your Investigator(s) will have access to the confidential information being collected.

However, the Regulatory Agencies, Institution Review Board and Ministry of Health will be granted direct access to your original medical records to check study procedures and data, without making any of your information public. By signing the Informed Consent Form attached, you or your legal representative is authorizing such access to your study and medical records.

Data collected and entered into the Data Collection Forms are the property of *Singapore General Hospital*. In the event of any publication regarding this study, your identity will remain confidential.

COSTS OF PARTICIPATION

No cost will be involved if you take part in this study.

No reimbursement will be pay out for your participation in this study.

WHO TO CONTACT IF YOU HAVE QUESTIONS

If you have questions about this research study and your rights or in the case of any injuries during the course of this study, you may contact the Principal Investigator *(A/Prof Marcus Ong at 6321 3590)*.

If you have questions about the study or your rights as a participant, you can call the SingHealth Centralised Institutional Review Board, which is the committee that reviewed and approved this study, the telephone number is 6323 7515 during office hours (8:30 am to 5:30pm).

CONSENT BY RESEARCH SUBJECT

Details of Research Study

Protocol Title:

Determining The Cost-Effectiveness Of Strategies To Improve Survival From Out-Of-Hospital Cardiac Arrest In Singapore

Principal Investigator:

A/Prof Marcus Ong Eng Hock
Department of Emergency Medicine, Singapore General Hospital
Tel: 6321 3590

Subject's Particulars

Name: NRIC No.:

Address:

Sex: Female/Male Date of birth _____
dd/mm/yyyy

Race: Chinese/ Malay/ Indian /Others (please specify) _____

Part I – to be filled by participant

I, (NRIC/Passport No.)
(Name of patient)

agree / do not agree *to participate in the research study as described and on the terms set out in the Patient Information Sheet. The nature of my participation in the proposed research study has been explained to me in*

by Dr/Mr/Ms
(Language / Dialect) *(Name of healthcare worker)*

I have fully discussed and understood the purpose and procedures of this study. I have been given the Participant Information Sheet and the opportunity to ask questions about this study and have received satisfactory answers and information.

I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reasons and without my medical care being affected.

I also give permission for information in my medical records to be used for research. In any event of publication, I understand that this information will not bear my name or other identifiers and that due care will be taken to preserve the confidentiality of this information.

_____ _____
[Signature/Thumbprint (Right / Left) of participant] (Date of signing)

Part II – to be filled by parent / legal guardian, where applicable

I, _____ hereby give consent for the above participant to participate in
(parent / legal guardian)
the proposed research study. The nature, risks and benefits of the study have been explained clearly to me and I fully understand them.

_____ _____
[Signature/Thumbprint (Right / Left) of parent /legal guardian] (Date of signing)

Part III – to be filled witness, where applicable

An impartial witness should be present during the entire informed consent discussion if a subject or the subject's legally acceptable representative is unable to read. After the written informed consent form and any written information to be provided to subjects, is read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally representative has orally consented to the subject's participation in the study and, if capable of doing so, has signed and personally dated the consent form, the witness should sign and personally date the consent form.

Witnessed by: _____ _____
(Name of witness) (Designation of witness)

_____ _____
(Signature of witness) (Date of signing)

Part IV– Investigator's Statement

I, the undersigned, certify to the best of my knowledge that the patient/patient's legally acceptable representative signing this informed consent form had the study fully explained and clearly understands the nature, risks and benefits of his/her / his ward's / her ward's participation in the study.

_____ _____ _____
Name of Investigator Signature Date