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**Termination of Resuscitation:  
Reducing Futile Transportation to  
Hospital for Out of Hospital Cardiac  
Arrests of Cardiac Aetiology**

M T House

DHC

2017

# **Termination of Resuscitation: Reducing Futile Transportation to Hospital for Out of Hospital Cardiac Arrests of Cardiac Aetiology**

M T House

A thesis submitted in partial fulfilment of  
the requirements of the University of  
Northumbria at Newcastle for the degree  
of Professional Doctorate

Research undertaken at the Faculty of  
Health & Life Sciences and in  
collaboration with North West Ambulance  
Service NHS Trust

April 2017

## **Declaration**

I declare that the work contained in this thesis has not been submitted for any other award and that it is all my own work. I also confirm that this work fully acknowledges opinions, ideas and contributions from the work of others. The work was done in collaboration with North West Ambulance Service NHS Trust.

Any ethical clearance for the research presented in this thesis has been approved. Approval has been sought and granted by the North West Ambulance Service NHS Trust on 11<sup>th</sup> October 2013, the Health Research Authority on 11<sup>th</sup> February 2014 and the Faculty Ethics Committee on 18<sup>th</sup> June 2014.

**I declare that the word count of this thesis is 48,872 words**

Name: Matthew House

Signature:

Date: 1<sup>st</sup> July 2017

## **Abstract**

**Background:** UK ambulance clinicians are able only to terminate resuscitation attempts that have resulted in an asystolic (flat line) cardiac rhythm, following twenty minutes of advanced life support. All other attempted resuscitations must be transported to hospital for further treatment. Despite this, there are still large numbers of patients transported to hospital who do not survive.

Thirteen studies were identified that purported to validate termination of resuscitation guidelines. This evidence could not be used to reduce the number of futile transportations to hospital of adult cardiac arrests of presumed cardiac aetiology within the geographical area of interest, due the variances in emergency medical systems.

**Methods:** Binominal logistic regression identified variables associated with outcomes in a dataset of 4,870 adult cardiac arrests of presumed cardiac aetiology (Phase 1). The clinical decision rule was validated retrospectively against an independent dataset of 2139 patients (Phase 2). It was then validated prospectively (Phase 3). Finally, the financial benefit of introducing the guideline was assessed. Assumptions were made on the potential resources required to treat each patient and the impact from an acute care perspective was assessed as the difference in cost when applying the guideline, compared to current practice.

**Results:** The clinical decision rule (terminate on scene if the initial rhythm was not shockable and there is no return of circulation) was shown in Phase 1 to have a specificity of 99.0% (95% CI: 97.7% to 99.7%) and sensitivity of 53.1% (95% CI: 51.6% to 54.6%). The transport rate was 52.4%. There were five (0.2%) unexpected survivors. This compared favourably with existing guidelines. In Phase 2 the

guideline recommended termination for 832 patients. Of these, 829 (99.6%) died and three (0.4%) survived (Specificity = 99.1%, 95% CI: 97.4% to 99.8%, Sensitivity = 46.5%; 95% CI: 44.1% to 48.8%). The transportation rate was 60.7%, which was lower than for existing guidelines when applied to the same dataset. Of 656 patients in Phase 3, the guideline recommended termination of 162 patients. None of these survived to hospital discharge (Specificity = 100%, 95% CI: 95.6% to 100%, sensitivity = 29.3%, 95% CI: 25.6% to 33.4%). The transportation rate during this phase was 75.3%. When plotted on a ROC space, the guideline showed better predictive power, when compared to existing guidelines. The minimum cost saving was shown to be £33,739 per 1000 adult OHCA patients currently transported to hospital.

**Conclusion:** Introducing the decision rule to the trust in question would reduce the number of transportations to hospital of adult patients suffering cardiac arrest of presumed cardiac aetiology. Further research is needed to apply the findings to other locations or emergency medical systems. In order to strengthen the validity of the tool, it should be assessed prospectively in either one large prospective study or several smaller studies, but within different settings. Ideally, to prevent bias, such a validation would be performed by a different research group

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## Abbreviations

AED	automated external defibrillator
ALS	advanced life support
BLS	basic life support
CDR	clinical decision rule
CEA	cost-effectiveness analysis
CI	confidence interval
cm	centimetres
CMA	cost-minimisation analysis
CPP	cerebral perfusion pressure
CPR	cardiopulmonary resuscitation
DNACPR	do not attempt cardiopulmonary resuscitation
ED	emergency department
EMS	emergency medical services
ERC	European Resuscitation Council
ETCO <sub>2</sub>	end tidal carbon dioxide
ICU	intensive care unit
ILCOR	International Liaison Committee on Resuscitation
ILS	Intermediate life support
in	inches
LOE	level of evidence
kg	kilogramme
LREC	local research ethics committee
min <sup>-1</sup>	per minute
mm	millimetres
mm Hg	millimetres of mercury
n	number
NPV	negative predictive value
OHCA	out of hospital cardiac arrest
OR	odds ratio
PEA	pulseless electrical activity
PICO	Population, Intervention, Comparator, and Outcome
PRF	patient report form
PPV	positive predictive value
pVT	pulseless ventricular tachycardia
R&D	research and development
RCUK	Resuscitation Council (UK)
RCT	Randomised controlled trial
ROSC	return of spontaneous circulation
SD	standard deviation
TOR	termination of resuscitation
UK	United Kingdom
VF	ventricular fibrillation
VT	ventricular tachycardia
vs	versus

## **Acknowledgements**

This thesis has been a constant pressure in my life for over four years. It has been there even when I was trying to forget it. Yet despite being my own project, it has impacted on a lot of people. My wife, Jo, has had to put up with having an absent husband for much of this time, as I spent hour after hour shut away reviewing statistics, or re-writing chapters. She has also had to put up with the inevitable mood swings that come from such a piece of work. For her understanding and constant support, I am eternally grateful.

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**“Despite rumour, Death isn’t cruel – merely terribly, terribly good at his job”**

Terry Pratchett <sup>1</sup>

## **1. Chapter One - Introduction**

Each year in the United Kingdom (UK) approximately 30,000 people receive resuscitation for an Out of Hospital Cardiac Arrest (OHCA), from which only about 7% survive to go home from hospital <sup>2</sup>. Data gathered by the Department of Health has shown that the vast majority of adults suffering an OHCA and who are transported to hospital do not survive <sup>3</sup>. The 2015 Resuscitation Council (UK) guidelines state that in most circumstances where return of spontaneous circulation (ROSC) is not achieved before transport and where Advanced Life Support (ALS) has addressed any potentially reversible causes, there is little benefit in transporting the patient to hospital <sup>4</sup>. However, the guidelines go on to say that there is little evidence to support the termination of resuscitation in all circumstances.

This thesis aims to determine whether it is possible to predict when a pre-hospital resuscitation attempt, of presumed cardiac cause, would not benefit from transport to hospital and can therefore be terminated safely, whilst minimising the potential for stopping the attempt during a potentially survivable resuscitation. The thesis will first explore the notion of death as a set point in time and discuss other theories as to the nature of death. It will then discuss the understanding of futility and its application as a medical term.

Current decision rules designed to allow the termination of resuscitation attempts before transport to hospital will then be explored. The thesis will then utilise data collected retrospectively to determine whether futile transport can be predicted, from various factors associated with OHCA. It will use this information to create a termination of resuscitation clinical decision rule (TOR CDR) for ambulance crews to use in order to determine when a resuscitation attempt should be terminated and

when it should be continued with transport to a receiving hospital for further treatment. This CDR will then be validated both retrospectively and prospectively to ensure that the proposed guideline is robust. Finally, an estimation of cost savings will be performed to examine the economic benefits of any proposed CDR.

## **1.1 Outline structure**

### **Chapter Two - Background**

This chapter provides the reader with background information on resuscitation. It reviews briefly the process by which death occurs, before discussing the practice of resuscitation in detail. It examines the theories on futility and how this is interpreted and applied to medical practice. The focus of this research is then discussed and justified, before the individual research aims and objectives are identified.

### **Chapter Three - Literature review**

This chapter addresses the first objective of the dissertation (i.e. to evaluate critically the existing validations of clinical decision rules relating to termination of resuscitation). It discusses the detail of the search strategy and defines how relevant articles were appraised. It then gives a comprehensive review of all relevant articles, before identifying areas in need of further research.

### **Chapter Four - Methodology and methods**

Various methodologies available to researchers are discussed in this chapter. A rationale is provided regarding the choice of methodology chosen for this study, and then the statistical methods employed at the various stages of the study are discussed. The issues regarding regulatory approval and ethical matters before commencing the study are identified and explained.



## **Chapter Five - Derivation of a clinical decision rule (Phase 1)**

This chapter tackles the second objective of the thesis (i.e. to derive a TOR CDR for adult OHCA of cardiac aetiology that is appropriate for use by pre-hospital clinicians, and which reduces the number of futile resuscitation attempts transported to hospital). It then goes on to discuss and justify the research strategy (a retrospective cohort study) as well as the data collection techniques used in the empirical collection of data for this study. Details of the analysis of the quantitative data are provided, and the resulting clinical decision rule is validated against the original dataset, and the results compared with other CDRs.

## **Chapter Six - Retrospective validation (Phase 2)**

This chapter addresses the third objective of the thesis (i.e. to validate retrospectively the clinical decision rule against an independent data-set of out-of-hospital cardiac arrests). It takes the decision rule derived in the previous chapter and retrospectively validates it against another, subsequent dataset. The methods are explained and the results are discussed in detail.

## **Chapter Seven - Prospective validation (Phase 3)**

This chapter addresses the third objective of the thesis (i.e. to validate prospectively the clinical decision rule). The study design (a prospective cohort study) is reviewed, before the statistical analysis is discussed in detail. The strengths and weaknesses of the study design are then analysed.

## **Chapter Eight – Estimate of cost savings**

Here the financial benefit of introducing the TOR CDR is assessed by using data gained from the outcomes of patients identified in phase 3. These costs are also assessed against the present situation and two other CDRs for comparison.

## **Chapter 9 - Conclusion**

This chapter reviews and summarises the specific objectives of this thesis and reaffirms the conclusions presented in earlier chapters. It highlights the strengths and weaknesses of the study and suggests areas for further research.

## **2. Chapter Two - Background**

### **2.1 When does death occur?**

The practice of resuscitation has been described as the clinician's attempt to wrest patients back from death <sup>5</sup>. Before discussing how resuscitation is attempted, it is important to understand what is meant by death, when it occurs and whether the answers to these questions may affect medical practice. These questions are not new to medicine. Celsus wrote in the seventh century "Democritus, a man of well merited celebrity, has asserted that there are in reality, no characteristics of death sufficiently certain for physicians to rely upon"(p166) <sup>6</sup>. Nevertheless, efforts have been made to describe death. Robert Veatch defines death as "a complete change in the status of a living entity characterised by the irreversible loss of those characteristics that are essentially significant to it" (p25) <sup>7</sup>.

Why a person should pass from being alive and fully functional to a state of death within minutes, often despite apparently successful resuscitation, is not clear. Death, or at least the point at which life ends, may to a certain extent be seen as a social construct. It may be influenced by religious, legal and political criteria. To understand death one must inevitably understand what is meant by life. The definition of life is central to religions across the world. This can be seen in many Western cultures when one considers attitudes to abortion and the rights of unborn children. Similarly, concepts of death are firmly rooted in both ancient and modern religious and political thinking. Often death is seen in terms of a journey, with the point of death being the time when a person travels to a new existence, beyond the physical. Nevertheless, this does not contradict the medical assertion given earlier that death is irreversible, as there is still the recognition that although the spirit moves on, the physical body of the corpse remains dead.

As death is closely linked with religious and cultural beliefs, the question of when death occurs and when it is acceptable to attempt resuscitation, or indeed terminate that attempt, are also closely linked to religion and culture. For example, Judaism holds a rigorous belief in the sanctity of life.

Biomedical matters in Jewish law are known as *halakhah* and there is literature covering all areas of medico-legal interest, including death. The definition of death becomes important, as it is prohibited to handle the dead on the Sabbath <sup>8</sup>. The central text of Rabbinic Judaism, the Talmud, gives two possible definitions of death. The first is the absence of breath in the nostrils, and the second is the absence of activity in the heart. There has been much debate as to which of these takes precedence, but the favoured position appears to be that breathing is the primary sign of life and so the absence of breath is a sign of death. Death therefore occurs when breathing completely and irreversibly ceases <sup>9</sup>. This definition does not recognise brain death as death. This has implications where patients' breathing and heart functions are being artificially maintained through the use of ventilators and other interventions, despite evidence of brain death.

Islam also has its own ethical framework for human life. The Quran says that "who so ever gives life to a soul, it shall be as if he had given life to mankind altogether" (5:32). Therefore attempts at resuscitation can be seen as an important part of the Islamic tradition. However, the determination of death is not universal within the tradition<sup>10</sup>. In Arabic, the word *al-mawt* means 'death' and it denotes a thing without a soul. According to Muslim scholars the processes of shrouding and other funerary requirements can only be initiated after 'complete death', when the soul has completely left the body. Although this term encompasses a myriad of interpretations, Muslim jurists appear to agree the main indicator for death is the

termination of respiration <sup>11</sup>. Brain death, in and of itself, however, is not considered indicative of death. If respirations and blood flow continue, even artificially, then it cannot be said for sure that the soul has departed. With this less strict interpretation, the Muslim tradition emphasises the need to consider the family's definition of death when making end of life decisions. Nevertheless this has led to reports that turning off the ventilator of a brain-dead relative was considered murder as relatives believed that whilst the body was still warm and had a heartbeat, it was therefore alive <sup>12</sup>.

Inherently, any medical definition will assume that death is an irreversible condition. Criteria and tests that define a patient's death should arguably ensure that once the requirements have been met, there can be no return, either with or without artificial assistance. Yet modern medicine has blurred the issue of what defines death, not least by the advances in intensive care medicine, where life support measures have become ever more advanced. Kellehear has noted that in European medicine, death was once defined as the point at which the heart stopped beating, but is now normally defined by brain death <sup>13</sup>. This is due in part to advances in intensive care medicine and the complex decisions that arise in relation to stopping medical interventions, such as artificial ventilation. A diagnosis of brain death uses elements such as fixed and dilated pupils, lack of eye movement and the absence of respiratory reflexes as determinants, rather than the presence of breathing or a pulse. He goes on to say that death has been complicated by the fact that people who are brain dead can be kept alive almost indefinitely by artificial means, and is further complicated because one in a thousand patients who are diagnosed as brain dead go on to survive for a period of time when their life support machines are switched off.

Parnia has written much about resuscitation and the point at which death may occur<sup>14</sup>. He has argued that death should no longer be seen as a specific moment in time. His position is that death is a process. Whatever the cause of death, the end result of the process is that there is an insufficiency in the supply of oxygen and nutrients to the individual cells of the body. This results in the organs stopping. However the key to this, claims Parnia, is that this process is not instant. He likens this to a full-brain stroke.

The processes that follow a stroke event are complex. During an ischaemic stroke, a blockage within a blood vessel in the brain occurs and reduces the oxygen available to cells (hypoxia). This leads to a reduction of the cellular chemical called adenosine triphosphate (ATP). ATP provides the energy to maintain ionic gradients across cell membranes, which is a requirement for normal cell function. Without it the processes that normally occur across the cell membrane is impaired, producing an increase in sodium within the cell. Increased sodium in the cell then results in increased water content, which causes swelling, or cytotoxic oedema<sup>15</sup>. Ischaemia also directly results in dysfunction of the brain's blood vessels. The blood-brain barrier breaks down within four to six hours after damage. Once this has happened, water and proteins flood into the area surrounding the cells and this increases the oedema further. The oedema then results in further brain swelling that reaches a peak at three to five days, but which can resolve over several weeks as the water and proteins are reabsorbed<sup>16</sup>. Specific genes are activated after a stroke that initiate the production of factors that sequentially cause increased inflammation and damage of the microscopic blood vessels within the brain<sup>17</sup>. As a result, the area around the point of damage, known as the ischaemic penumbra, is increasingly affected. This

causes it too to become damaged and die within hours of the stroke's onset. The dead tissue eventually degenerates in a process known as liquefaction necrosis.

Parnia argues that death should be seen in the same way as a stroke. However, rather than being a localised event, death is a 'whole-brain' stroke, as there is a lack of supply to the whole brain when the heart stops beating <sup>18</sup>. As all brain cells become deprived of oxygen, the stroke process described above occurs across the whole brain. As with a stroke, there is a transition process whereby this damage is at first reversible and then irreversible. This process, as with a stroke can go on for many minutes or hours after death has started. However, unlike the localised tissue ischaemia of a stroke, a return of oxygen to the brain, or tissue reperfusion, following cardiac arrest cannot be considered a definitive therapy. A return of spontaneous circulation (ROSC) will be achieved in about 30% of all cardiac arrest victims, as the heart starts beating again, but only about 6% will survive <sup>2</sup>. Nearly 60% of those patients resuscitated from cardiac arrest will ultimately die from neurological dysfunction caused by the arrest process <sup>19</sup>.

This concept that death is a process supports the theories of Lamb. He has advocated that death should be seen as the "irreversible loss of function of the organism as a whole...(rather than)... death of the whole organism" (p14) <sup>20</sup>. He argues that as cells from different organs continue to function long after the organism has ceased to function, criteria for determining the death of the whole organism could not be met without tests for putrefaction. On the other hand, loss of the organism's function as a whole can be determined with precision, and is a biological concept, which can be determined by clinical criteria and tests.

Following on from the work of Lamb and Parnia, the traditional concepts of determining death by reference to the cessation of cardiac and pulmonary functions have arguably never adequately characterised death. Rather, they are an indirect way of determining the death of the whole organism. That is to say that diagnosing death on the basis that the heart and lungs have stopped is effectively no more than a prediction that brain death will occur, on the grounds that brain death follows inevitably from the permanent cessation of cardio-pulmonary function. As Puccetti rationalised; strictly, people do not die of heart attacks or lung cancer: These events merely destroy the cardiac or respiratory function, which in turn causes the death of the whole body, through lack of oxygen<sup>21</sup>. Death of the heart and lungs is not in itself death, but a cause of death. Nevertheless, the brain is a critical organ that controls and regulates the bodies' other organs. Permanent loss of cardiac function may therefore be seen as an indicator of a permanent loss of brain function, which is death. Thus, although the point of death itself is difficult to define, cardiac arrest has been defined by the international consensus workshop as "cessation of cardiac mechanical activity, as confirmed by the absence of signs of circulation"<sup>22</sup>, which therefore leads to sudden death, unless reversed promptly.

## **2.2 Resuscitation**

As death starts with the cessation of heart function, resuscitation is the practice of attempting to restart the heart, in order to prevent the death process. The science of resuscitation has a long history. For much of human history, death was viewed as irreversible. The Greek authority, Galen (AD130-200) conducted experiments on animals and taught that the heat of life was created in the furnace of the heart. He believed that this fire was extinguished at death and this was one of the reasons death was seen as irreversible. There has been a great deal of development in the



practice of resuscitation medicine since these early days. However, the clinical problems surrounding resuscitation practice have been poorly understood and the science surrounding it has been limited.

The modern practice of resuscitation is considered to have started with the work of Kouwenhoven, Jude and Knickerbocker, who described the method of closed-chest cardiac compression, which is recognised today as cardiopulmonary resuscitation (CPR) <sup>23</sup>. It has been said that in the field of resuscitation there is a surprisingly limited amount of evidence, with very little of this being of high-level <sup>24</sup>. It is rationalised that this is due partly to the legislation surrounding consent, which places restrictions on research in both the USA and Europe. In turn, this has led to the continued reliance on traditional treatments in the absence of new research developments. The lack of reliable evidence led amongst other things to the creation of the International Liaison Committee on Resuscitation (ILCOR). ILCOR was formed in 1992, and sought to identify, collect and review the international science and knowledge pertaining to the practice of resuscitation and to offer treatment and practice recommendations <sup>24</sup>. This has led to ILCOR becoming a forum for cooperation between the various resuscitation organisations throughout the world, and an institution for the development of a consensus approach to practice.

The first international consensus on resuscitation was established with Guidelines 2000 for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care, established following a review of all the available literature <sup>25</sup>. The process was repeated in 2005, 2010 and again in 2015 <sup>26</sup>. The latest guidelines resulted from a long process, during which ILCOR task forces identified specific areas relating to resuscitation practice, and then reviewed and evaluated all the available literature. This in turn allowed the final Consensus Conference to achieve agreement and

produce the consensus statements on resuscitation. Both the European Resuscitation Council (ERC) and the Resuscitation Council UK (RCUK) have used these consensus statements to update their own treatment and practice guidelines that are relevant for European and UK populations respectively <sup>27,4</sup>.

The practice of resuscitation can be broadly defined as either basic life support (BLS), or advanced life support (ALS). BLS is the provision of external cardiac compressions, with or without mouth-to-mouth ventilations <sup>26</sup>. Increasingly, BLS has also included the use of automated external defibrillators (AEDs), which are capable of providing defibrillation, but which do not require the user to have training in their use, as they are fully automated and provide the user with voice prompts. ALS incorporates BLS, but adds to that the use of advanced airway interventions and the use of cardioactive drugs, such as adrenaline and amiodarone <sup>26</sup>. In the UK pre-hospital environment, Paramedics provide ALS, whereas other ambulance providers, such as technicians and volunteer first responders are limited to BLS.

Although CPR was first seen as a dramatic life-saving intervention, its promise has waned somewhat with experience. In the UK, sudden cardiac arrest accounts for around 100,000 deaths per year <sup>28</sup>. Of these, it is estimated that 60,000 occur out of hospital and about 45% of these are treated by emergency medical services (EMS)<sup>29</sup>. Unlike portrayals in films, where 68% of OHCA result in survival <sup>30</sup>, only about 24% of patients who have had resuscitation efforts initiated or continued by the ambulance service following a cardiac arrest will achieve ROSC by the time they are transported to hospital and about 6% of them will survive to hospital discharge <sup>31</sup>. Despite these figures, resuscitation of OHCA remains an important part of an ambulance service's *raison d'être*. If an OHCA is suspected when the ambulance service is called, it results in a 'Red 1' response, which is the highest level of

response, and for which each ambulance service in England and Wales is targeted to arrive on scene within eight minutes, in 75% of all cases. Also both ROSC and survival are reported annually as part of the NHS England Ambulance Quality Indicators: Clinical Outcomes <sup>2</sup>.

Cardiac arrest presents initially as one of four heart rhythms, or cardiac arrhythmias. The first two are the so-called shockable rhythms, which include ventricular fibrillation (VF) and pulseless ventricular tachycardia (pVT), both of which can be resolved by defibrillation, or an electrical charge passed through the heart muscle. The others are the so-called non-shockable rhythms. Asystole is the flat line rhythm, most associated by lay people as cardiac arrest, and pulseless electrical activity (PEA). The latter is indicated by electrical activity in the heart, without the corresponding pulse. The treatment options available for resuscitation depend on the cardiac arrhythmia that caused the cardiac arrest, and any subsequent changes in that rhythm.

VF has been described as an irregular, almost random electrical activity within the heart, which produces no useful contractions <sup>32, 33</sup>. It has been argued by some authors that VF may actually be seen to be an organised pattern made up of either multiple propagating wavelets of activity, or alternatively as spiral wave re-entry patterns <sup>32</sup>. However, it is beyond the scope of this thesis to discuss these theories further. pVT is a cardiac rhythm which originates in the lower parts of the heart, the ventricles rather than the sino-atrial node, which is the natural pace-maker of the heart. It is a regular rhythm, unlike VF, and produces a rate of about 120-220 min<sup>-1</sup>. pVT may result from several cardiac abnormalities, including re-entry of the electrical pathway, or from the enhanced automaticity of the ventricular pacemaker cells in the heart, which means that the cells of the ventricles fire off signals before

they receive messages from the pace-maker <sup>22</sup>. pVT is more commonly associated with serious underlying heart disease, though it does occur in patients with no underlying cardiac pathology. The rhythm itself can maintain a pulse for a period of time, though it may also cause haemodynamic compromise in its own right, or may develop into VF if left untreated <sup>32</sup>.

PEA, which was previously known as electromechanical dissociation (EMD), is defined as organised electrical activity in the heart, but with no detectable pulses <sup>34</sup>. Aufderheide has shown that a PEA may be classified as true PEA, pseudo-PEA and normotensive PEA <sup>34</sup>. True PEA has the presence of electrical activity, but there is no corresponding myocardial (heart muscle) contraction. In pseudo-PEA, there is some myocardial contraction, but the resultant pressure in the blood vessels is so small that it can be measured only by invasive monitoring. In normotensive PEA the myocardium contracts in time with the electrical rhythm, but no detectable pulses are present.

All cardiac arrest events will deteriorate into asystole, if left untreated. Asystole is recognised by a 'flat line' trace on the electrocardiogram (ECG) and can be defined as the absence of any heart rhythm <sup>35</sup>. However, this definition does not necessarily identify the intricacies of asystole. Ornato and Peberdy have commented that a slow, 'bradyasystolic' rhythm can include long periods of absent heart rhythm with only occasional, isolated beats originating from the ventricles (idioventricular beats) <sup>36</sup>. Also, it must also be noted that an asystole is not the same thing as a dead heart. Asystole can occur early in an arrest and is potentially, though rarely, reversible. However, as an arrest persists, severe cardiac ischaemia results unless effective cardiac compressions are administered. This in turn leads to progressive myocardial wall thickening causing the ventricular cavity to reduce in size. This results in a

“stony heart”, which has been shown in porcine models to result in a “strikingly firm and contracted heart” (p1008) <sup>37</sup>.

Definitive information about an initial arrhythmia at the time of collapse could only be recorded if an implanted device was in place at the time of death <sup>38</sup>. However, VF is often quoted as the most common cause of sudden cardiac arrest <sup>39, 40</sup>. Nevertheless, recent studies have shown that the incidence of VF as the initial rhythm in out of hospital cardiac arrests has declined in recent years <sup>32</sup>.

A population based study from Seattle, Washington has seen the adjusted annual incidence of cardiac arrest where VF is the first identified rhythm decrease by about 56% from 1980 to 2000, or 43% when adjusted to include only those cardiac arrests of presumed cardiac cause <sup>33</sup>. A similar Swedish study, looked at 19,215 sudden deaths between 1991 and 2001 and found that there was a decrease in VF among patients with a bystander witnessed cardiac arrest at home from 45% in 1991 to 28% in 2001 ( $P < 0.0001$ ) <sup>34</sup>. By contrast, a prospective population-based cohort study of out of hospital cardiac arrests covering a population of 8.8 million in Osaka, Japan found that the age adjusted annual incidence of witnessed VF increased significantly from 2.0% to 3.3% ( $p$  for trend, 0.002) over the seven years of study. However, only 20% of those cardiac arrests which were of presumed cardiac aetiology presented with an initial rhythm of VF, whereas 55% were asystole and 25% were PEA <sup>35</sup>.

Due to the nature of VF, with its inevitable decline into asystole if left untreated, it may be argued that response times of the initial medical responder have an effect on the first recorded cardiac rhythm, with a reduction in the occurrence of VF as response intervals increase. One retrospective, observational study sought to address this possibility. It looked at patients with out of hospital cardiac arrests of

presumed cardiac aetiology over a ten year period and investigated changes in incidence and survival, of those patients where there was an identifiable rhythm and where resuscitation was attempted. Although the presence of witnesses to the arrest event, public location, and shorter response intervals from the emergency services were found to be factors predictive of VF/pVT, none of these factors were found independently to explain the decrease in the incidence of this category of arrests. Over the course of the study, response intervals were shorter than those previously reported and they continued to decrease over the course of the study period. There was also no decrease in the number of arrests in public locations <sup>41</sup>. It has been hypothesised that the reduction in VF is due to the introduction of new treatment regimes, particularly the use of antiarrhythmic medications, which allow patients with ischaemic heart disease to live longer. If these patients do eventually suffer a cardiac arrest, their heart disease has by this time reached its end stage, and so PEA or asystole is more likely than VF <sup>34</sup>.

There have been reports of VF spontaneously reverting to a normal, or sinus rhythm, with an associated cardiac output <sup>42</sup>. However, these are accepted to be the exception to the rule and for the vast majority of cardiac arrests, intervention is required to reverse the condition. Current UK and European treatment guidelines for cardiac arrest emphasise the 'chain of survival' <sup>4,27</sup>. This term was coined to recognise that survival from cardiac arrest is improved when a particular sequence of events is followed <sup>43</sup>. Initially the sequence included early recognition and activation of emergency medical services, basic life support (BLS), early defibrillation and early advanced life support (ALS). However, it has since been adapted by replacing the term early ALS with "post resuscitation care" <sup>24</sup>. Yet it is noted that despite advances in resuscitation practice and continued emphasis on this 'chain of survival', survival

from out-of-hospital cardiac arrest to hospital discharge remains at about 7% throughout the UK <sup>29</sup>.

One component common to all resuscitation attempts is the provision of effective external cardiac compressions, or cardiopulmonary resuscitation (CPR). The importance of effective cardiac compressions has been evident for some time. In 1936 Wiggers suggested that “(internal) cardiac massage which sustains coronary flow be started as soon as possible after the onset of fibrillation and be continued until the electrodes are ready for application to the heart” <sup>40</sup>.

The exact methods by which compressions maintain blood flow are uncertain and may be variable. Early studies using echocardiograph equipment placed in the oesophagus suggested a cardiac pump theory <sup>44</sup>. This theory argues that compressions squeeze the heart’s ventricles between the sternum and the vertebrae of the back, which causes pressure within the heart. This pressure forces the mitral and tricuspid valves in the heart to close, and directs the blood from the ventricles into the pulmonary and peripheral circulation. During the decompression phase the pressure is reduced, and the ventricles are allowed to refill with blood. However, Rudikoff, Maughan, Effron *et al.* subsequently noted that whilst they applied a constant compression force during forced ventilation, a compression started at end-inspiration resulted in greater arterial pressure and blood flow, even though the sternum was farther from the vertebral column at this point <sup>45</sup>. They also noted that in patients with flail (detached) sternums there was no increase in arterial blood pressure during chest compressions. This was counter-intuitive, as the added movement of the chest that this condition allows should have increased the potential pressure of the heart against the vertebrae. This was therefore not consistent with the cardiac pump theory. A later canine study provided persuasive evidence that

pressures created in the vasculature depended on increased pressure in the chest cavity, or intrathoracic pressure <sup>45</sup>. Rudikoff, Maughan, Effron *et al.* argued that the increased pressure caused during compression acted not just on the heart but also on the other intrathoracic organs. This pressure then transmits directly to extrathoracic arteries, which causes the arterial blood flow. Backward flow through the venous system is prevented because the thin-walled veins, which are without musculature, collapse due to the intrathoracic pressure. Once the compression is released, and pressure in the chest falls below venous pressure, the veins reopen. This allows blood to flow back into the chest and refill the heart, allowing the cycle to continue. However, the authors conceded that due to the differences in thoracic anatomy between canines and humans, caution was required if generalising their “thoracic pump” findings to man. Nonetheless, the hypothesis was supported by Criley, Niemann, Rosborough *et al.* who reported that patients having cardiac arrest in the catheterisation laboratory maintained blood flow without external compressions by repetitive coughing, which similarly increased thoracic pressure <sup>46</sup>.

It has latterly been argued that neither of these hypotheses fully explains how external cardiac compressions maintain blood flow. This has led to the “lung pump” theory. This theory uses the principle of a cyclical pump, and suggests that chest compressions increase intrathoracic pressure, which affects all intrathoracic organs, including the lungs. The pulmonary valve in the right side of the heart closes during a compression, due to the extra pressure in the lungs. This prevents the blood returning to the right side of the heart. Instead, blood within the vasculature of the lungs is forced to exit through the left side of the heart and into the peripheral circulation. As the compression is released and intrathoracic pressure falls, the blood



volume in the lungs is restored by flow from the right side of the heart as the tricuspid and pulmonary valves open <sup>47</sup>.

Whichever model is correct; there is now a consensus that cardiac compressions must be continued throughout cardiac arrest events. Compressions provide both cerebral and myocardial perfusion pressure. Perfusion pressure of an organ is equal to the arterial pressure providing blood to that organ, minus the relative venous pressure of the blood leaving the same organ. So, cerebral perfusion pressure is established by the difference between mean arterial pressure and intracranial pressure. During compressions the arterial pressure is provided by each external compression and this provides the perfusion pressure. This process applies to all organs except the heart. The heart's blood flow originates at the base of the large artery, the aorta, at the point it leaves the heart. The blood fills the coronary arteries, which provide the heart tissue with blood during the decompression phase of CPR, as pressure is released. Coronary perfusion pressure is therefore calculated as the pressure difference between the aorta and right atrium during the decompression phase of CPR.

Myocardial perfusion is essential for ROSC to occur <sup>48</sup>. Animal studies have shown that during prolonged cardiac arrest, survival is directly related to the coronary perfusion pressures generated by CPR <sup>49</sup>. Also, VF can be delayed from deteriorating into asystole if coronary perfusion pressure is maintained <sup>50</sup>. However, it is not certain whether coronary perfusion pressure is causally related to ROSC, or whether it is simply an indication of overall vascular status. Nonetheless, it appears that a coronary perfusion pressure of 15 mm Hg is necessary for ROSC, which is approximately 20% of normal myocardial flow <sup>48</sup>.

Although myocardial perfusion is essential for ROSC to occur <sup>48</sup>, perfusion of the brain is critical to neurological function <sup>50</sup>, and is also a predictor of ROSC. The most important factor in determining cerebral perfusion during cardiac arrest is the arterial pressure generated during external chest compressions <sup>51</sup>. Rubertsson and Karlsten measured cerebral perfusion during CPR using a porcine model. Manual CPR produced at best about 40% of baseline blood flow <sup>52</sup>. CPR in humans has been shown to create mean cerebral perfusion pressure (CPP) of 30+/-8 mmHg when started immediately upon arrest <sup>53</sup>.

However, canine studies conducted by Shaffner, Eleff, Brambrink *et al.* found that a six minute delay in initiating CPR then required a higher CPP to restore cerebral blood flow, and following a twelve minute delay, cerebral blood flow could not be restored, even with a CPP of 35 mm Hg <sup>54</sup>. They suggested that this may have been due to the swelling of the tissues that surround the capillaries of the brain, which in turn limits flow at low perfusion pressures, as discussed in earlier in this chapter. The effect of any delay in starting CPR is particularly relevant to resuscitation the prehospital environment, where skilled help is not necessarily at hand.

Nevertheless, the importance of early CPR is a cornerstone of the 'chain of survival' concept <sup>4</sup>. The definitive contribution it makes to survival is difficult to establish, as studies in this area suffer from the limitation that the interval from collapse to the arrival of help in OHCA is difficult to quantify accurately. Early work by Larsen, Eisenburg, Cummins *et al* estimated that for patients in VF, the chance of a successful outcome was reduced by 2.3% for every minute delay in CPR <sup>55</sup>. However, Valenzuela, Roe, Cretin *et al* used a logistic regression model that included terms for both interval to CPR and interval to defibrillation, and found that the odds of survival decreased by 10% for every minute that CPR was delayed <sup>56</sup>.

Whilst cardiac compressions will maintain a degree of artificial circulation during a resuscitation event, the RC(UK) emphasise that a responder must consider and treat any reversible causes, in order to successfully resuscitate a patient <sup>4</sup>. The reversible causes are commonly referred to as the 4Hs and 4Ts. The 4Ts refer to: hypoxia (low oxygen levels in the blood); hypovolaemia (reduced blood volume); hypo or hyperkalaemia (lowered or raised potassium levels), or other metabolic disorder; and hypothermia. The 4Hs refer to: thrombosis (a blocked blood vessel in either the heart or the lungs); tension pneumothorax (a condition where the lung function is reduced due to excess pressure in the space between the lung and the chest wall); cardiac tamponade (a condition where blood escapes into the area around the heart, causing pressure and reducing the pumping action of the heart); and toxins. Though a suspicion may be raised by the circumstances of the particular patient or situation, the recognition and treatment of these reversible causes is a challenge in the prehospital environment <sup>4</sup>.

For patients in VF/pVT rhythms, the present resuscitation guidelines recommend early defibrillation <sup>24</sup>. This has been described as the “single most important factor in surviving cardiac arrest due to VF” <sup>57</sup>. Beck described the first use of defibrillation in a human patient in 1947 <sup>40</sup>. The shock was administered directly to the patient’s heart during an operation for sternal resection. Like much of resuscitation practice, the science behind defibrillation is not fully understood <sup>57</sup>. As previously mentioned, VF is a chaotic rhythm, caused by irregular, almost random electrical activity within the heart. Following experiments on cardiac fibrillation in canine models, it is believed that defibrillation causes a critical mass of cardiac cells to depolarise, or stop, and those that are not depolarised are not sufficient in number to continue the

chaotic fibrillation. This allows the heart's natural pacemaker , the sinoatrial node, to retake control and regulate a normal rhythm <sup>58</sup>.

It is generally believed that the timing of any defibrillation is important, with early defibrillation proving more successful. This is explained by the 3-phase model of CPR described by Weisfeldt and Becker <sup>59</sup>. This model describes the progression of resuscitation pathophysiology and its influence on correct resuscitation interventions. The so-called electrical phase persists for the first 4 minutes of VF. In this phase prompt delivery of defibrillatory shocks is recommended for correction of the arrhythmia. This is why there is emphasis on public defibrillators and the prompt delivery of shocks in current resuscitation guidelines <sup>60</sup>.

The circulatory phase lasts for approximately 4-10 minutes of VF and is characterised by depletion of energy-rich substrates, increased tissue acidosis and cellular dysfunction. It has been suggested that at this stage, CPR is of more importance, as it provides circulation of blood and a partial restoration of essential substrates including oxygen, as well as the removal of damaging metabolic factors that have collected during ischaemia.

The final stage is the metabolic phase, which develops after about 10 minutes of an arrest. During this phase it is suggested that tissue injured as a result of global ischaemia result in the circulation of metabolic factors that then cause additional injury beyond the effects of any local ischaemia. Weisfeldt and Becker suggest that therapeutic hypothermia may protect against the effects of the metabolic phase, and suggest that the continued use of vasoconstricting drugs, such as adrenaline, which is recommended by current ALS guidelines, may have a harmful effect at this stage

by promoting organ ischemia, particularly in the visceral organs of the abdomen. This, they argue, leads to decreased survival.

Despite this assertion, current guidelines recommend the use of adrenaline for all prolonged resuscitation attempts <sup>26</sup>. Adrenaline has both alpha and beta-adrenergic actions, which means it affects the contractility of the heart as well as constricting peripheral blood vessels. It has been used in ALS for nearly forty years. As already discussed, CPR is used to maintain blood flow to the heart and brain before ROSC, and this represents only about 30% of normal values at best <sup>61</sup>. It is thought that adrenaline improves this effect, through its action on adrenergic receptors, by increasing arterial and arteriolar vasoconstriction, which results in an increase in peripheral pressures <sup>62</sup>. Its continued use in resuscitation is not without controversy <sup>63</sup>. There is some evidence that the use of adrenaline for OHCA was associated improved overall survival and neurologically intact survival among patients presenting with non-shockable rhythms <sup>64</sup>. However, one prospective, randomised controlled trial showed that whilst improvements in ROSC are achieved with the use of intravenous adrenaline, there was no significant improvement in survival to hospital discharge (10.5% vs 9.2 %  $P= 0.61$ ), but was unable to determine whether the effects on survival were due only to the adrenaline <sup>65</sup>.

As already noted, the use of adrenaline may promote organ ischaemia and have a negative effect on resuscitation <sup>59</sup>. Nonetheless, despite these issues, the present guidelines continue to advocate the use of adrenaline for resuscitation, due to the accepted benefit in short-term outcomes (achieving ROSC and admission to hospital) and the lack of sufficient evidence to determine the effects on survival to discharge and neurological outcome <sup>26</sup>. At the time of writing, there is a large

randomised controlled trial being conducted in the UK, which hopes to answer that question<sup>66</sup>.

This section has given a brief overview of current resuscitation science and practice. It has shown that the science of resuscitation has a long history, but despite the advances over that time, the general principles have remained unchanged for decades. Furthermore, it has highlighted that the advances in practice that have been introduced have not seen dramatic improvement in patient outcomes over the same extended period. This may suggest that certain resuscitation attempts are unlikely to be successful, despite the best efforts of clinicians. The next section will look at the notion of futility in medicine and how it applies to the resuscitation scenario.

### **2.3 Futility**

Having established that successful resuscitation attempts are rare, and survival rates have remained relatively unchanged for some time, it may be possible to determine at which point there is no reasonable chance of reversing the inevitable outcome of a cardiac arrest. That is to say, further resuscitation would be futile. In the pre-hospital environment, this equates to terminating efforts on scene, as opposed to transporting the patient to a hospital with continued resuscitation efforts. This section looks at the concept of futility and how it applies to clinical practice.

The word futility comes from the Latin word 'futilis', which means leaky. In Greek mythology, the daughters of Danaus were sentenced to spend eternity in Hades, carrying water in leaky sieves. They represent the futility of a repetitive task that can never be completed and their story suitably conveys the meaning of the term. It implies more than just something improbable, rare or unusual. An action is futile if it

will not achieve its aims, no matter how often it is repeated. Also, futility must be distinguished from the notion of hopelessness, which is a subjective attitude, based on an emotional reaction. By contrast, futility relates to the objective possibility of a specific endpoint.

The discussion of futility, when associated with medical procedures is wrought with ethical dilemmas. It is linked with questions as to the goals of medicine and what is acceptable if those goals are not, or cannot be realised. However, unlike scientific absolutes, medical futility is a term based on ethical choices as defined by society. So society's expectations of medicine will invariably affect its position on medical futility. The World Medical Association (WMA) states that futile medical treatment is one which "offers no reasonable hope of recovery or improvement...(or from which)...the patient is permanently unable to experience any benefit" (p46) <sup>67</sup>. It goes on to say that a physician is under no obligation to offer a patient futile or non-beneficial treatment.

Decisions on when to commence resuscitation attempts or when to cease those that have been started can be complex. For UK ambulance clinicians, the criteria indicating when a resuscitation attempt should not be initiated are relatively simple and clear in emergency situations, and are present in current guidelines <sup>68</sup>. These guidelines identify those conditions that are unequivocally associated with death, such as massive cranial and cerebral damage, decomposition or rigor mortis. They also identify situations where there is no realistic chance that resuscitation would be successful. These include an interval of fifteen minutes since the patient collapsed, with no bystander CPR and the presence of an asystolic heart rhythm. The presence of do not attempt CPR (DNACPR) orders would also prevent the initiation of resuscitation. However, even these decisions may be complicated by the legalities

surrounding consent and capacity, and the physical presence of DNACPR paperwork. Indeed, much of the literature surrounding futility and resuscitation decisions is based on issues around DNACPRs. However, it is beyond the scope of this thesis to discuss these in detail as they pertain to decisions on when to start, rather than when to stop resuscitation.

The decision to cease resuscitation efforts that have already started, due to apparent futility of those efforts can be a hard decision to make. As well as medical considerations, often the expectations of relatives or other bystanders can influence those decisions. Marco found that of 1,256 American Emergency Physicians, 62% had made resuscitation decisions out of the fear of litigation or criticism, rather than for any expected medical benefit <sup>69</sup>. As well as any practical considerations, the question of ethics surrounds this decision-making process. All policies, procedures and individual decisions must comply with human rights. Those relevant to decisions about resuscitation include the right to life; to protection from inhuman or degrading treatment; and to be free from discriminatory practice in respect of these rights <sup>70</sup>.

Although there are many schools of ethics, the most common in Western culture is based on the four principles of biomedical ethics, introduced by Beauchamp and Childress <sup>71</sup>. The four key principles are beneficence, non-maleficence, justice and autonomy. Beneficence directs that the clinician must provide benefit, but must balance that benefit against any risks. Non-maleficence means doing no harm. Both beneficence and non-maleficence can be seen as supporting the decision to stop a resuscitation attempt, when it has become futile. Not only are patently futile resuscitation attempts unlikely to provide any benefit for the patient, the practice of aggressive resuscitation can be seen to 'harm' the patient, in terms of fracturing ribs during CPR, and the invasive techniques of airway management and intravenous



access. Nevertheless, the principle of autonomy could be seen as an argument against a decision to stop efforts as it is made, necessarily, without the consent of the patient (excluding obviously, those DNACPR decisions made before the arrest).

The concept of patient autonomy includes a patient's right to be a fully informed participant in any decision-making in relation to their treatment, and this includes the right to refuse treatment, even if this is life-saving. However, that does not include the right to demand treatment that is futile <sup>72</sup>. In an early paper on futility, Murphy, although discussing the decision to start resuscitation, argues that the administration of futile interventions is irresponsible. He goes on to argue that the notion of patient autonomy should be reconsidered in these circumstances, and that such decisions can be made without consulting them or their relatives <sup>73</sup>. Younger responded to this paper, saying that this approach is a lapse back into the outdated notion of paternalism <sup>74</sup>.

Tomlinson and Brody acknowledged the argument that such a robust application of futility in decision-making could be seen as a return to paternalistic medical practice <sup>75</sup>. However, they argued that this is not the case: suggesting instead that if a treatment is objectively futile, then to even offer this as an option is to breach the patient-provider relationship, as it wrongly suggests that there is something to be gained from that treatment. They use this rationale to suggest that by restricting futile options patient autonomy is actually enhanced, as it prevents the giving of false hope. However, they add the caveat that futility is not an arbitrary standard, but is a measure of social judgement or 'reasonableness'.

Despite the inevitability of death, it has been argued that modern Western culture no longer accepts death as a natural part of life <sup>76</sup>. As noted earlier, this view is

strengthened by the unrealistic success rates of resuscitation successes in modern media <sup>30</sup>. Even in modern medicine, with its continuing emphasis on technology, death is being seen increasingly as a disease to be conquered <sup>20</sup>. The ethicist Daniel Callahan has argued that modern medicine has a tendency to see death not as a biological fact, but as a moral evil and medical failure <sup>77</sup>. This has resulted *inter alia*, in further developments in medical technology and intensive care medicine based on the desire to extend life at all costs. This can result in the bodies of patients who have suffered brain death being kept alive artificially, through the use of ventilators and other technologies.

One of the many moral dilemmas that this leads to is determining when resuscitation efforts should be discontinued. The complexity of this question is compounded by the lack of certainty around benefit in modern medicine. In early nineteenth century medicine, all treatments were, by the definitions of the day, effective. There were limited expectations as to the effects of interventions, and so these expectations were invariably met. For example, emetics, as the name suggests, would cause vomiting, or purgatives would cause laxation <sup>78</sup>. The medical theories of the time were concerned with no more than these outcomes and so it was considered that as these treatments were effective, they were therefore also beneficial.

However, modern medicine makes a distinction between effectiveness and benefit. By accepting that the definitive goal of a treatment is to improve the patient's prognosis, comfort, or general health, then a treatment that fails to do this should be considered futile, even though it may produce a measurable effect. Therefore effect and benefit are distinct. A point is reached where the chance of success is so small, or the benefits so indiscernible that they would be futile to attempt.

For the practice of resuscitation, the attempt is futile if it will be of no benefit in prolonging life. The question then is whether this may go as far as to include the quality of life that is preserved or gained. Plunkitt, Matar and Basta have written that “CPR is not indicated unless there is a reasonable hope for a conscious life with a chance that the patient will be able to pursue and achieve some degree of happiness” <sup>79</sup>.

However, Baskett, Sanders and Steen have countered this by saying that such rationales are not universal. They maintain that there is no agreement on whether the goal of resuscitation is the prolonging of life or some other perceived notion of ‘quality of life’ <sup>80</sup>. Moreover, the inclusion of ‘quality of life’ implies a value judgement. They go on to say that futility, to have any meaning, must be quantified. However, there are difficulties with this. Whilst a number of factors may need to be taken into account when determining whether a resuscitation attempt should be stopped, many of these will be unknown, particularly during an out-of-hospital arrest, where the patient’s background, their standard of living and their co-morbidities, for example, may not be known and are difficult to establish in the heat of the moment. Some facts, when they are known, may directly affect decision making. For example, findings such as hypothermia or opiate overdose are legitimate cause to change the approach to stopping or extending resuscitation efforts. Other decisions in the field may be based on emotional criteria, such as the decision to continue for longer because the patient is known to the responding team, or the patient’s relative youth.

These purely emotional decisions, argues Baskett, Sanders and Steen, do not stand up to evidence-based examination <sup>80</sup>. What is more, they may result in the overtreatment of objectively futile attempts, and conversely the under-treatment of those for whom there is less emotional attachment. Some would argue that neither of

these positions can be supported ethically. Rather, decisions on futility should be made objectively, following an honest assessment of possible outcomes <sup>81</sup>.

In the pre-hospital environment, prolonged resuscitation efforts and subsequent transport of those cardiac arrest patients who will inevitably die, will undeniably divert limited medical assets away from other patients who might depend on them. These resources are not limited to the ambulance service, but include the hospital resources that are required to manage the patient once transported.

Additionally, it is known that emergency ambulance transports are in themselves dangerous. Between 1991 and 2000 in USA, emergency transportation resulted in 27 EMS deaths and the deaths of 275 pedestrians and other road users <sup>82</sup>. Therefore, the emergency transport of patients with no chance of survival diverts resources and constitutes a risk to ambulance clinicians and bystanders, without the necessary benefits to justify this risk. However, these risks must be balanced against the possibility of stopping a resuscitation attempt on a patient who may survive if that attempt was continued and they were transported to hospital.

There is nevertheless, a caveat when considering this dilemma. When weighing up these conflicting interests, it is important not to confuse the decision to terminate or transport, with issues of limited resources, which Jecker and Schneiderman call distributive justice <sup>83</sup>. Resources may be impacted by the decision, but do not drive it. Decisions based on the needs of the wider population are in effect decisions on rationing resources, and are necessarily based on discrimination and value judgements. They are nonetheless important decisions. Healthcare is under pressure constantly to provide more and better care for less money. This may well influence decisions on options, which may provide limited improvements to certain

patient groups, and is recognised by the World Medical Association as a serious consideration when choosing treatment options <sup>67</sup>.

For the purposes of this thesis, however, futility is an individual, patient-based judgement and does not make comparisons between patients. It is not a decision based on a shortage of resources, even though the cessation of futile efforts may well increase resources available elsewhere in the system. Rather, futility must be based on the objective fact that the treatment is not medically beneficial and is based solely on the patient in question <sup>84</sup>.

Futility in this context means that continued efforts will not reverse the patient's condition. This concept has continued to be the subject of much debate in recent years. Increasingly, medical professionals have argued that, in line with the goals of medicine since the times of Hippocrates, there is no moral obligation to treat patients when interventions cannot produce a sufficient quality of life. This notion can be traced back to Plato's Republic, where he cites that

"Asclepius...taught medicine for those who were healthy in their nature but were suffering from a specific disease...For patients whose bodies were always in a state of inner sickness, he did not attempt to prescribe a regimen, for that would make their life a prolonged misery . . . medicine was not invented for them and they should not be treated even if they were richer than Midas." <sup>85</sup>

So it can be seen that futility has both a quantitative dimension (where the probability of achieving the desired result is unreasonably small) and a qualitative one (where the best possible outcome will not benefit the patient). This thesis will concentrate on the quantitative dimension, which will be discussed later. Nevertheless, it is important to understand the qualitative dimension. If one is creating a CDR for TOR,

it can be based on the premise that anyone who leaves hospital alive is a successful resuscitation.

However, an alternative approach is to measure those who survive with meaningful neurological function. By this approach, survival in itself is not considered a success, but rather the quality of a patient's subsequent life is considered important. What is meant by meaningful in this context is subjective. It will depend on society's perspective as well as that of the individual patient.

Some have argued that the Glasgow Coma Scale (GCS) could be used to determine meaningful in this context <sup>86</sup>. The GCS is a tool created in 1974 as a way to classify the level of consciousness of patients with brain injury <sup>87</sup>. The scale measures three factors: eye opening; verbal response; and motor response. This produces a score of between three and fifteen, with three being deeply unconscious and fifteen being normal brain functioning. Haukoos, Lewis and Niemann have suggested that a GCS of equal to or greater than thirteen indicate a good neurological outcome as this would show that the patient was awake, could follow commands, and were at worst disoriented and conversant <sup>86</sup>.

An alternative to the GCS is to use the cerebral performance category (CPC) scale. This scale categorises patients on a scale of one to five: 1, good cerebral performance; 2, moderate cerebral disability; 3, severe cerebral disability; 4, vegetative state; and 5, death. Using this scale, CPC scores of 1 and 2 are usually considered as 'good' outcomes, whereas CPC 3, 4 and 5 are considered 'poor' outcomes <sup>88</sup>. However, it has been argued that that there is no standard method of determining CPC scores, which can lead to variation of interpretation <sup>89</sup>.

A third option is to use the modified Rankin Scale (mRS). First developed by Rankin<sup>90</sup> and subsequently modified by Farrell, Godwin, Richards, *et al*<sup>91</sup>, this scale uses six categories of zero to five: 0, No symptoms; 1, no significant disability; 2, slight disability; 3, moderate disability; 4, moderately severe disability; and 5, severe disability. Although this scale does include descriptions of limitations in activity and changes in lifestyle, which assist with classification, it has also been criticised for being subjective and open to interpretation<sup>92</sup>.

That there are competing methods of defining the qualitative aspects of survival emphasises the difficulty in assessing these outcomes. The counter-argument to their use is that decisions made on qualitative grounds are again simply a new instance of medical paternalism and that quality of life decisions are inherently personal so should not be decided by medical practitioners. Brody, however, makes the interesting distinction between pre-emptive 'do not attempt cardio-pulmonary resuscitation' (DNACPR) orders and the decision to cease resuscitation attempts. He notes that whilst those arguing against futility say that any decision to enter a DNACPR should not be made without the patient's consent, these same people do not object to clinicians making a decision to stop resuscitation after a prolonged attempt<sup>93</sup>.

Nevertheless, the Utstein resuscitation registry templates for OHCA recommend that neurological outcome may be reported using either the CPC or the mRS, although they also recognise that ROSC and long-term survival (reported either as survival to hospital discharge or 30 day survival) are the core reporting outcomes<sup>94</sup>.

In England and Wales the law, as defined by the Mental Capacity Act 1985, gives primacy to patient autonomy. This requires that the patient has the right to be fully

informed of all aspects of clinical decision making relating to their treatment, and to be a participant in those decisions. This includes the right to refuse treatment even when this is recommended and could be life-saving. This notion of autonomy has, to a greater or lesser extent eclipsed the principle that futile treatments are not obligatory.

Bernard Lo has argued that a unilateral decision by clinicians to withhold or cease a treatment is justified where that treatment has no pathophysiologic rationale, or where such a treatment has been started but the patient has failed to respond <sup>82</sup>. However, he goes on to distinguish this from other uses of the term futility, such as when the likelihood of success is very small, but not zero. This, argues Lo, can lead to problems with the concept of futility. However, Tomlinson and Brody pose the argument that just as a doctor can refuse to give a patient antibiotics, because the chance of them improving a cold are very remote, so too if likelihood of survival from cardiac arrest is very small, then it is for the medical practitioner to determine that and make the decision <sup>95</sup>. They argue that in principle, the value judgment on the withholding of antibiotics is no different to the withholding of CPR. If can be made in the one case, why not in the other?

Lantos, Singer, Walker *et al* had previously advocated caution with such an approach. For them, a futile therapy is simply the end of a spectrum of therapies with low efficacy, the evidence for which can become confused by statistical errors, linguistic misunderstandings, or from disagreements about the goals of the therapy in question <sup>96</sup>. Decisions on whether a treatment is futile may be based on imprecise data, or may be influenced by a clinician's own belief system. This has led Brody to suggest that if decisions are made in only the clearest cases, then there will be an inevitable slide into making unjustified decisions in the less definite situations <sup>93</sup>.



There is the risk that although an analysis of futility may appear to be based on a patient's interest, it is in fact, driven by the interests of the clinician and others.

The term futility suggests a dichotomous decision: either a treatment is futile, or it is not <sup>97</sup>. However, one may more correctly see futility in terms of scale. The question remains, therefore, as to whether the notion of futility can be quantified. That is to say, is it possible to determine how many times a technique or procedure would have to fail before it can be said to be futile? It has been argued that logically, just because patients with certain conditions have never survived resuscitation in the past, then one cannot conclude that it is not a possibility that the next patient will survive, even though it is highly improbable <sup>98</sup>. This logic then leads to the recognition of a minimum acceptable probability of success that is greater than zero <sup>95</sup>. This is accepted by some, who have argued that futility should extend beyond absolutes, and should be the result of institutional or professional consensus, rather than the decision of the individual clinician <sup>99</sup>. Moreover, it has been said that without an explicit definition, there is the danger that the threshold may creep up and encompass situations where success is a possibility <sup>100</sup>.

This is of particular importance in the pre-hospital environment, where decisions need to be made quickly by relatively junior clinicians and with some degree of certainty. Paramedics, although a registered profession in the UK, are not doctors. To expect the decision to be left to them, in the heat of the moment may be construed by some to be unfair, and on the evidence of the ethico-legal dilemmas already discussed, wrought with potential difficulties. There is little chance to consult with others when decisions on terminating a resuscitation attempt are to be made whilst that attempt is in progress. So, if this decision could be made for them and presented in the form of guidelines, then they could concern themselves with the

practicalities of the situation, without being encumbered with the burden of complex ethical decision-making.

The European Resuscitation Council has stated that “CPR that has no chance of success in terms of survival or acceptable quality of life is pointless and may violate the right for mercy and dignity in the face of death” (p305) <sup>101</sup>. It goes on to propose that institutional guidelines for pre-hospital TOR are required to reduce variances in decision-making. However, Ardagh has argued that futility is subject to such variations of interpretation that it is unlikely a consensus definition that is applicable to every patient undergoing resuscitation will ever be achieved <sup>102</sup>.

In 2002, Löfmark and Nilstun attempted to produce a model for futility <sup>103</sup>. They reviewed 43 articles and despite creating such a model, suggested that there was no need to define futility in order to make an acceptable decision for a given situation. Nonetheless, various writers have sought to apply definitions of quantitative futility to the practice of resuscitation.

At one extreme, the American Heart Association suggested in 1992 that a futile resuscitation attempt is one where “there have been no survivors reported under the circumstances in well-designed studies” <sup>104</sup>. Others have taken a less restrictive approach. For example, Murphy has suggested that futility was observed in their series of patients when survival after CPR was no better than 2% <sup>105</sup>, and Lantos, Singer and Walker, *et al* when survival was no better than 7% <sup>106</sup>. Schneiderman and Jecker have written extensively on the subject. They started with a general understanding of medical futility, which they defined as “any effort to provide a benefit to a patient that is highly likely to fail and whose rare exceptions cannot be systematically produced “ <sup>84</sup>. They then attempted to quantify this. They proposed

that where a treatment had been of no use in 100 cases, then it could be deemed to be futile. They argue that although the previous 100 cases do not necessarily mean the treatment will never work, it serves as an estimate of the effectiveness of that treatment. They go on to argue that whilst clinical trials are not available for every circumstance, the experienced clinician should use their own experience to create these so-called “futility characteristics”, which appears to step beyond their otherwise objective approach to the question of futility. Moreover, even their statistical approach is not without critics. Helft, Siegler and Lantos maintain that, despite its claimed objectivity, this quantitative definition of futility is in fact subjective <sup>107</sup>. They also note that individual patients may consider a treatment with a 1% chance of success as worthy of attempting, particularly if the alternative was death.

Nevertheless, Lawrence, Schneiderman and Jecker support their position with statistical probability. Although they have accepted that the proposed 1% definition is arbitrary, they argue that it can be viewed in the same way one assesses the evidence in scientific papers: if there have been no successes in 100 consecutive cases, then statistically, one can be 95% confident that no more than 3 successes would occur in each 100 comparable trials (3 successes per 100 trials is the upper limit of the 95% CI) <sup>108</sup>. They support this argument by suggesting the question of futility is not concerned with asking about the certainty of a treatment not working, but rather about how many times a treatment should be seen to fail before it is agreed that it does not work. This argument is persuasive and 1% has since been acknowledged by many as the working definition of medical futility <sup>109,110,111,112</sup>.

## **2.4 Termination of resuscitation**

The concept of futility is important to any discussion on stopping resuscitation attempts. Larkin has emphasised that decisions around TOR are both simple and complex <sup>113</sup>. He argues that the decision is a simple one in that the decision itself can be, and often is, made very quickly when all those on scene agree that nothing more can or should be done (which may or may not be with reference to a TOR guideline). However, it is also complex in that there is a great deal of uncertainty around the science of resuscitation, as has been previously discussed, and often the circumstances of a particular cardiac arrest are unknown. Furthermore, it has been said that survival from OHCA is a reflection of the EMS attending the incident and the subsequent hospital treatment, and that any TOR rule is in danger of becoming a self-fulfilling prophecy <sup>114</sup>. The counter-argument to this is that whilst all patients suffering OHCA deserve an appropriate attempt at resuscitation, there are those for whom nothing is to be gained from transport to hospital <sup>115</sup>.

Nevertheless, Pepe has suggested that decisions on TOR are often determined by family and clinician comfort levels and the on-scene environment <sup>116</sup>. This is supported by a systematic review conducted by Anderson, Gott and Slark that suggests that the reasons given by clinicians to stop a resuscitation attempt are many and varied and include internal factors, such as the clinician's experience, as well as external factors, such as the expectations of family members and perceived patient characteristics <sup>117</sup>.

There have been many published studies relating to the predictors of success for resuscitation of OHCA. An early study by Silfvast looked at asystole as a defining characteristic of non-survival and recommended that resuscitation should be stopped

in adult patients, who were not hypothermic and were in an asystolic rhythm, providing that the airway had been secured and intravenous access had been achieved <sup>118</sup>. This is understandable, as an asystolic heart has no on-going electrical activity. However, whilst Pepe, Levine, Fromme *et al* found there were no survivors out of 106 asystolic patients with unwitnessed OHCA for whom no CPR was initiated, there was a 1.6% survival rate for those incidents where resuscitation was attempted <sup>119</sup>. This is supported by the work of Engdahl, Bang, Lindqvist *et al*, who found that survival amongst 1,635 patients presenting with an initial asystole was 2% <sup>120</sup>. This increase may be due to the improvement in resuscitation practice in the intervening years. Nevertheless, it is now commonly accepted that regardless of initial rhythm, if a patient suffering OHCA of presumed cardiac aetiology is in asystole following vigorous ALS, there is nothing to be gained by transporting that patient to hospital <sup>27</sup>.

Response interval has been another suggested predictor of futility <sup>121</sup>. The response interval is the period of time between a patient's collapse, and when a responder arrives at the patient to commence resuscitation. Although response intervals are undeniably important, detailed analysis has shown that survival from OHCA does not decline at a constant rate following the arrest <sup>122</sup>. This had led Gold, Fahrenbruch, Rea, *et al* to conclude that models should not include factors external to the patient. They argue that incorporating physiological changes following a cardiac arrest are a more accurate way to ascertain survival rates <sup>121</sup>. Despite this conclusion, others have looked at factors relating to the circumstances of the arrest to determine outcomes. Spaite, Hanlon, Criss *et al* suggested that unwitnessed OHCA were less likely to survive than witnessed ones ( $p < .001$ ) <sup>123</sup>. This was supported by Stratton and Niemann, who found no survivors to hospital discharge from 104 patients

suffering unwitnessed OHCA, irrespective of initial rhythm <sup>124</sup>. Although the sample size was small, these results support the 'chain of survival' principles noted earlier. However, subsequent studies have shown that, whilst bystander-witnessed arrests are more likely to result in survival (OR 2.0, 95% CI = 1.6 to 2.7), the variable is not in itself a predictor of futility (survival in this study = 1.36%) <sup>125</sup>.

In 1993 Bonnin, Pepe, Kimball *et al* performed the first large-scale prospective study to find criteria for terminating resuscitation for OHCA <sup>126</sup>. They prospectively monitored the outcomes from 1461 OHCA and found that patients who achieved five-minute ROSC on scene had approximately 32 times greater odds of survival compared with a patient who did not achieve ROSC. They concluded that apart from patients in persistent VF, transport of OHCA was futile if no ROSC was achieved on scene. A more recent prospective population-based observational study in Japan challenges this conclusion. Goto, Maeda and Nakatsu-Goto studied specifically those patients transported to hospital without ROSC <sup>127</sup>. They found that of 398,121 patients, 7,532 (1.89%) were alive one month after the event, despite being transported without ROSC. Although this study does not record survival to hospital discharge, it does suggest that lack of prehospital ROSC is not in itself a predictor of futility.

Similar large-scale studies have suggested that whilst there is no single variable that can confidently predict futility, a combination of variables may be sufficient to do so. Two recent termination rules for EMS personnel used multiple variables to predict successfully which OHCA patients will not benefit from being transported to ED for continued resuscitation <sup>111, 112</sup>. These rules use clinical variables to determine suitability for termination in the field. For BLS rescuers, these variables are: arrest not witnessed by EMS, no defibrillation, and no ROSC in the field <sup>111</sup>. For ALS

providers the variables include the previous three and add no bystander CPR and the arrest was not witnessed by EMS <sup>128</sup>.

In 2010 a systematic review and meta-analysis by Sasson, Mary, Rogers *et al* looked at the associations between key clinical factors of survival from OHCA using over 30 years of data <sup>129</sup>. This study, which involved more than 142 000 patients, found conclusively that bystander CPR, initial shockable rhythms, and ROSC were predictors of survival in the prehospital setting. Of the 36 studies found to consider bystander CPR, the pooled odds ratio for survival amongst this group compared with those who did not receive bystander CPR ranged from 1.23 (95% CI; 0.71 to 2.11) in the studies with the highest baseline survival rates to 5.01 (95% CI; 2.57 to 9.78) in the studies with the lowest baseline rates. Of the 58 studies that considered initial cardiac rhythm, the pooled odds ratio for survival among patients with an initial shockable rhythm compared to those found in non-shockable rhythms ranged from 2.91 (95% CI; 1.10 to 7.66) in the studies with the highest baseline rates of survival to 20.62 (95% CI; 12.61 to 33.72) in the studies with the lowest baseline survival. Twelve studies were found that reported on prehospital ROSC. The pooled odds ratio for survival for patients who achieved prehospital ROSC compared to those who did not ranged from 20.96 (95% CI; 7.43 to 59.13) in those with the highest baseline survival rates to 99.84 (95% CI; 14.30 to 696.89) in the studies with the lowest baseline rates of survival.

This systematic review and meta-analysis concluded the most powerful criterion by far that was associated with survival from OHCA is ROSC and that failure to achieve ROSC before transport suggests that the patient is unlikely to survive to hospital discharge. Nevertheless, despite these findings, the authors note that there were large variances in outcomes, which appear to be attributable to the different EMS

systems across the studies. Moreover, whilst the review identifies those variables which are associated with survival, there was no attempt to derive a TOR CDR as a result of these findings.

More recent work has been done on the value of end-tidal carbon dioxide (ETCO<sub>2</sub>) in predicting survival. ETCO<sub>2</sub> measures the concentration of carbon dioxide at the end of an exhaled breath, and is an indication of cardiac function and pulmonary blood flow. It has been shown in a small prospective study that in patients undergoing resuscitation for OHCA, the ETCO<sub>2</sub> values of those who achieved ROSC were significantly higher than those of the patients who died <sup>130</sup>. If ETCO<sub>2</sub> remains under 10 mmHg during CPR, it is strongly associated with non-survival <sup>131</sup>. This work shows potential, but has yet to be developed fully.

The studies discussed above suggest that it is possible to determine variables within a particular EMS system that may be useful in determining futility, provided there is an acceptance that futility does not predict absolutes. Although it may be argued that unless a TOR CDR can determine futility with absolute certainty, then it should not be considered; throughout the history of resuscitation practice, there have been unexpected survivors.

In a recent Danish study, Rajan, Folke, Kragholm *et al* it was shown that even where resuscitation continues for over 25 minutes, 20.4% of patients achieved ROSC, though only 13.8% survived beyond 30 days, compared to 59.6% of patients who achieved ROSC in under five minutes<sup>132</sup>. Nevertheless, there have been several reported cases where prolonged resuscitation attempts have resulted in unpredicted survival. Parnia has discussed the case of one individual from England, who underwent three and a half hours of resuscitation, before his heart was started and



went on to make a full recovery <sup>18</sup>. Although the circumstances surrounding this particular event were unusual, in that the patient was suffering from profound hypothermia at the time of his collapse, the case emphasises the difficulties in prognostication, following a cardiac arrest.

Pena, Aedo and Palomino performed a systematic review of the literature and found 38 examples of what is known as the 'Lazarus Phenomenon' <sup>133</sup>. This phenomenon refers to the unexpected recovery of a patient for whom resuscitation was not started, or efforts have been stopped, due to perceived futility. For these patients, the time interval between collapse or termination of resuscitation efforts and subsequent ROSC ranged from a few seconds to 33 minutes. Pena, Aedo and Palomino postulate that one reason for these unexpected events is the incidence of hyperinflation of the chest, caused by over-enthusiastic ventilations during resuscitation. The increased intrathoracic pressure caused by this hampers venous return, which in turn causes a decrease in cardiac output and coronary perfusion. As artificial ventilation is stopped, there is a decrease in intrathoracic pressure, which may result in successful mechanical pumping activity of the heart. If this theory is accepted, then the 'Lazarus effect' may be seen a result of poor resuscitation technique, rather than any unexpected physiological response. However, this theory does not explain the three cases where no resuscitation was attempted (although at least one of these patients was fitted with an internal pace-maker). Nevertheless, Pena, Aedo and Palomino conclude that incidents of what they describes as 'spontaneous auto-resuscitation' either after life support techniques have been terminated, or in the absence of any such techniques are considered rare, but may be a lot more common than expected.

Whatever the cause, these events serve to highlight the fallibility of any TOR guideline and the difficulties in determining with certainty when a resuscitation attempt becomes futile. However, to refrain from implementing any TOR guideline, due to a very remote possibility of survival would in itself be unethical. Nevertheless, decisions on futility must be clearly defined so as to prevent overenthusiastic application of the concept. If a decision is made using the term futility, every effort should be made to search for the best possible proof to back up that decision, to reduce the prognostic uncertainty, even if it can never be completely eliminated <sup>134</sup>. Whether sufficient evidence can be established and verified, which will allow pre-hospital clinicians to maintain aggressive resuscitation attempts for those who may benefit, whilst identifying those for whom further attempts and transport to hospital are futile, will form the basis of this thesis.

As this thesis develops, it is important to acknowledge that TOR guidelines do already exist in UK ambulance Trusts, in line with the UK Ambulance Services Clinical Practice Guidelines <sup>135</sup>. These guidelines allow for the recognition of life extinct in circumstances where resuscitation should not be attempted. They also allow for the termination of resuscitation in the presence of asystole, following twenty minutes of ALS (except in cases of hypothermia, drowning, poisoning, overdose or pregnancy). Therefore, this thesis is aiming to identify futile transportation of patients who are out with this group. These will be patients with a PEA, or persistent VF/pVT despite ongoing resuscitation.

It is also important to note that OHCA can be caused by numerous events. These may be related to trauma, medication, respiratory issues, or a number of other factors. Each of these factors bring with them different treatment options both within the pre-hospital environment and within hospital. This thesis will look only at those

OHCA which are of presumed cardiac aetiology. That is to say sudden cardiac death presumed to have been caused by malignant ventricular arrhythmia. For these purposes, an OHCA will be presumed to have been of cardiac origin, unless there is some evidence to the contrary. Similarly, the resuscitation of children has a different approach to that of adults. This is due in part to the fact that the majority of children have healthy hearts, and so cardiac arrests in this group are likely to have been caused by something other than a cardiac event <sup>26</sup>. Therefore this thesis will limit itself to adult patients and will not seek to determine a guideline for the termination of resuscitation in children.

## **2.5 Overall research aim and individual research objectives**

The overall aim of this research is to advance an understanding of when it is appropriate to terminate attempts at resuscitation for adult patients suffering OHCA of presumed cardiac aetiology, and when transport to ED is appropriate. It will aim to determine whether there is a subset of patients who are not included in existing UK ambulance service TOR guidelines and are currently transported to hospital following OHCA of presumed cardiac aetiology, for whom it can be said that transport to a receiving hospital with ongoing resuscitation is futile and that all further resuscitation can be terminated on scene. Specifically, the objectives of this research are:

1. To evaluate critically the exiting validations of clinical decision rules (CDRs) relating to termination of resuscitation.
2. To derive a TOR CDR for adult OHCA of cardiac aetiology that is appropriate for use by pre-hospital clinicians, and which reduces the number of futile resuscitation attempts transported to hospital.

3. To validate retrospectively the CDR against an independent data-set of out-of-hospital cardiac arrests
4. To validate prospectively the CDR, to ensure that ambulance clinicians are able to apply the TOR CDR and identify those patients for who transport to hospital is futile.
5. To estimate the cost savings of introducing the TOR CDR.

## **2.6 Value of this research**

This research is valuable for a number of reasons. The literature review will show whether TOR CDRs have been validated in pre-hospital care systems. In particular, it will aim to determine whether these rules are applicable to the UK ambulance Trusts, and whether the rules add to the TOR guideline currently in use, which allows for TOR of asystolic patients only.

The subsequent empirical research is required to establish whether a termination of resuscitation guideline can be derived and validated, which accurately identifies those patients for whom further resuscitation and transport to hospital are futile, and whether ambulance clinicians are capable of identifying those patients in accordance with the guidelines. The RC(UK) states that, “In most patients where ROSC is not achieved on scene, despite appropriate ALS and treatment of any potentially reversible causes, little is to be gained from transferring these patients to hospital.”<sup>4</sup> As shown above, the vast majority of these patients are presently transported to the emergency department (ED), which places an unnecessary burden on both the ambulance service and the receiving hospitals.

The question that needs to be answered is whether a decision rule can be established that identifies resuscitation attempts that are ultimately futile, and allows ambulance clinicians safely to terminate the attempt. This thesis will attempt to answer that question. Throughout this process, the figure of 1%, as proposed by Schneiderman and Jecker will be used to define futility. In the next chapter, the existing evidence will be reviewed and TOR guidelines that have been validated for use in practice will be discussed.

### **3. Chapter Three - Literature review**

In the previous chapter it was established that the majority of pre-hospital resuscitation attempts do not result in survival, despite transport to hospital. It was also established that it is possible to define futility in medical treatment scenarios. In this chapter, there will be a review of existing TOR CDRs that have been validated, and which purport to characterise futile resuscitation attempts.

#### **3.1 Search strategy**

A literature search was performed in January 2014. A preliminary search using the Web of Knowledge search engine confirmed that there was a large amount of research available on the subject of termination of resuscitation, with 476 results reported. However, the focus of this literature review is the validation of CDRs. Therefore an approach was taken that aimed to balance the need for high recall combined with high precision in the search strategy. To do this, the approach described by Hek and Langton was employed <sup>136</sup>. First an initial search was conducted to capture any material that appeared to have a focus on the validation of CDRs for the termination of resuscitation. This ensured high recall. Then all remaining articles were appraised in order to filter less relevant ones. This ensured that only those studies that were concerned with the validation of TOR CDRs, rather than the derivation of them, were included for detailed review. This process ensured high precision of the remaining articles.

In order to formulate a search question for the initial search, the PICO (Population, Intervention, Comparator, and Outcome) format was used <sup>137</sup>. Using this format, the question used was:

“During adult cardiopulmonary resuscitation, can termination of resuscitation clinical decision rules predict futile resuscitations?”

The search strategy included a search of three scholarly databases (Table 1) as well as direct searches of two academic and professional journals considered to have particular relevance (Table 2). No systematic reviews were found on the Cochrane database. Searches of Medline and the Web of Knowledge were conducted (Appendix 1). The titles of all articles found using this strategy were assessed for relevance. Where the content of an article was evidently unrelated to the validation of a CDR, it was discarded at this stage. Then the remaining articles were filtered following a review of their abstracts, leaving only those directly relevant to this study.

Additionally, to support these searches and ensure full capture, a ‘snowball’ search as described by Maskrey and Greenhalgh<sup>138</sup> was undertaken of the references cited by each of the papers already retrieved. This aimed to identify any potentially valuable literature that had not been captured, or had been rejected during the initial filter.

Databases	
Cochrane	Web of Knowledge
Medline	

**Table 1 - Databases searched**

Journals	
Resuscitation	Circulation

**Table 2 - Professional journals searched**

### 3.2 Inclusion criteria

All peer reviewed studies that were attempting to validate termination of resuscitation decision rules were included.

### **3.3 Exclusion criteria**

Studies and articles were excluded using the following filters:

1. Abstract only studies, letters, editorials, conference information and non-peer-reviewed articles.
2. Studies where the termination of resuscitation rule was designed for paediatric patients.
3. Non-English language articles were also excluded, as no reliable and accessible translation service is available for this thesis.

### **3.4 Evidence appraisal**

Following the selection procedure, all remaining studies were reviewed in detail to assess methodological quality. There are various tools used to measure the quality of published research. Many of these are inconsistent in their classifications and subsequent recommendations <sup>139</sup>. However, this thesis is concerned with the validation of a CDR, and specific requirements have been proposed to determine the methodological standards of these. A CDR has been defined as “a clinical tool that quantifies the individual contributions that various components of the history, physical examination, and basic laboratory results make toward the diagnosis, prognosis, or likely response to treatment in an individual patient” <sup>140</sup>. Once CDRs have been formally tested, they simplify clinical decision making. They also improve the accuracy and of a clinician’s diagnosis and prognosis. They are of particular use in complex decision making, such as in the practice of resuscitation.

As with other areas of research numerous tools are available to evaluate the derivation and validation of CDRs <sup>141-144</sup>. Although these vary in their detail, there are common elements. Firstly, the CDR should be derived as a result of clinical need. Any mathematical techniques used to derive the rule should be adequately defined.



Both the outcome and the predictor variables need to be defined, and the latter should be reliable. That is to say, they should be reproducible. Finally, and arguably most importantly, a rule should be validated.

Validation ensures the CDR can be generalised to the patient population <sup>140</sup>. It ensures that there is a causative association between the predictors and outcome and that they have not occurred by chance. It also ensures that the predictors are not due to peculiarities of the population or dataset from which the CDR was derived, or to other aspects of the study design.

There are various strategies when performing a validation. In order of increasing rigor, these are temporal, geographical, and domain validations<sup>145</sup>. Temporal validations are often (though not necessarily) completed by the same investigators, in the same locations, but at a later date to the derivation of the guideline. Geographical validations, as the name implies, are ones which uses a population from a different location. A domain validation is the most rigorous, but difficult to achieve for out of hospital patients, as it requires a different setting (such as primary care vs. secondary care).

McGinn, Guyatt, Wyer *et al* also define four levels of validation <sup>141</sup>. Level 1 is the most robust and equates to a CDR that has undergone at least one prospective validation in a different population to the derivation, and one impact analysis. It must also demonstrate a change in clinician behaviour as well as beneficial consequences. A level 2 validation is one which has been proven in either one large prospective study or has been validated in several smaller studies, but within different settings. A level 3 validation is one that has utilised only one narrow, prospective sample. Finally a level 4 validation has used only split samples, large

retrospective databases, or statistical techniques. McGinn, Guyatt, Wyer et al argue that all but level 4 validations can result in a decision rule being implemented, with varying degrees of certainty. A level 4 validation, they contend, requires further validation before being implemented into practice.

### **3.5 Search results**

In all, 86 articles were identified during the initial search (Appendix 2). An initial review of the titles, excluded 47 articles from further appraisal. The remaining 37 appeared to address the research question. A further eight studies were included for review: Three of these were included following a review of citations, and five were found as a result of alerts placed on searches, and were captured after the initial search was conducted.

A review of the abstracts resulted in 14 studies being reviewed in detail. A summary of each study is provided in Appendix 3 (see also Tables 3-5). An additional study was identified, which had performed a structured review of four CDRs<sup>146</sup>

**Table 3 – BLS TOR validations**

Rule	Study Design	Author	Year	EMS system	Total Numbers	TOR positive	TOR Survivors	Transport Rate	CDR Criteria Level
<b>BLS TOR</b>	Prospective, observational validation	Morrison et al <sup>147</sup>	2006	EMT (AED)	1,240	62.6% (n=776)	0.51% (n=4)	35.60%	2
	<b>Retrospective cohort analysis</b>	Richman et al <sup>148</sup>	2008	EMT-Basics, EMT-Intermediates EMT-Paramedics	2,180	n= 804 (adjusted)	0.12% (n=1)	46.80%	<b>CDR Level 4</b>
		Ong et al <sup>110</sup>	2006	BLS with AEDs	13,684	50.4%(n=6,908)	0.04%(n=3)	49.5%.	
		Ong et al <sup>149</sup>	2007	BLS with AEDs	2,269	68.7%(1,559)	0.38% (6)	31.30%	
		Sasson et al <sup>150</sup>	2008	Not specified	5,505	47.1%(n=2,592)	0.2% (n=5)	52.90%	
		Morrison et al <sup>128</sup>	2007	Paramedic	4,673	48% (n=2,263)	Nil	51.6%.	
		Morrison et al <sup>151</sup>	2009	Tiered:Police, Fire, defib-only EMTs, Paramedic	2,415	54.3%(n=1,302)	Nil	45.6%.	
		Ruygrok <sup>152</sup>	2009	Fire-based first responders providing BLS, including use of AEDs, and ALS paramedics	715	32% (n=231)	Nil(good neurological)	70.2%.	
		Kajino et al <sup>153</sup>	2013	Emergency Lifesaving Technicians	151,152	74.9% (n=113,140)	0.2%(n=193) (good neurological)	25.10%	
		Cheong et al <sup>154</sup>	2016	Intermediate life support service, including AED, laryngeal mask airways (LMAs), administration of IV adrenaline and a limited range of other medications.	2,193	64.3%(n=1,411)	0.4% (n=5)	35.60%	
		Chiang et al <sup>155</sup>	2015	Fire-based first responders providing BLS, including use of AEDs, and ALS paramedics	1,727	62.5% (n=1,080)	1.7% (n=29)	37.50%	

**Table 4 – ALS TOR validations**

Rule	Study Design	Author	Year	EMS system	Total Numbers	TOR positive	TOR Survivors	Transport Rate	CDR Criteria Level
<b>ALS TOR</b>	<b>Retrospective cohort analysis</b>	Skrifvars <i>et al</i> <sup>156</sup>	2010	Nurses or paramedics and Emergency Medical Technicians	20,705	26.4%(n=5,466)	0.04%(n=2)	73.60%	<b>CDR Level 4</b>
		Morrison <i>et al</i> <sup>128</sup>	2007	Paramedic	4,673	30% (n=1,425)	Nil	69.9%.	
		Sasson <i>et al</i> <sup>150</sup>	2008	Not specified	5,505	21.7%(n=1,192)	Nil	78.30%	
		Morrison <i>et al</i> <sup>151</sup>	2009	Tiered:Police, Fire, defib-only EMTs, Paramedic	2,415	31%(n=743)	Nil	69.00%	
		Ruygrok <sup>152</sup>	2009	Fire-based first responders providing BLS, including use of AEDs, and ALS paramedics	715	23% (n=162)	Nil(good neurological)	77.30%	
		Kajino <i>et al</i> <sup>153</sup>	2013	Emergency Lifesaving Technicians	137,986	27.1% (n=41,030)	0.1% (n=37)	70.30%	
		Chiang <i>et al</i> <sup>155</sup>	2015	Fire-based first responders providing BLS, including use of AEDs, and ALS paramedics	240	34.1%(n=82)	4.9% (n=4)	65.80%	
		Cheong <i>et al</i> <sup>154</sup>	2016	Intermediate life support service, including AED, laryngeal mask airways (LMAs), administration of IV adrenaline and a limited range of other medications.	2,193	27.3%(n=587)	0.2% (n=1)	73.20%	
		Verhaert <i>et al</i> <sup>157</sup>	2016	Paramedic	598	6%(n = 35)	Nil	94%	

**Table 5 – Remaining TOR validations**

Rule	Study Design	Author	Year	EMS system	Total Numbers	TOR positive	TOR Survivors	Transport Rate	CDR Criteria Level
Not EMS witnessed Not bystander witnessed Aged 78 years or older, or initial rhythm asystole	Retrospective cohort analysis	Ruygrok <sup>152</sup>	2009	Fire-based first responders providing BLS, including use of AEDs, and ALS paramedics	715	5% (n=39)	Nil(good neurological)	94.5%.	CDR Level 4
<b>Asystolic arrests:</b> Delay in ambulance exceeding 15min, No ROSC despite 20min of ALS. <b>Witnessed PEA:</b> Delay in ambulance exceeding 15min, No ROSC within 20min of ALS. <b>Un-witnessed PEA:</b> No ROSC within 10min of ALS		Skrifvars <i>et al</i> <sup>156</sup>	2010	Nurses or paramedics and Emergency Medical Technicians	20,705	54.6%(n=1,1315)	0.5% (n=57)	45.30%	
Asystole and call time > 8 mins		Ong <i>et al</i> <sup>110</sup>	2006	BLS with AEDs	13,684	9.4%(n=1,293)	0.08%(n=1)	90.60%	
		Ong <i>et al</i> <sup>149</sup>	2007	BLS with AEDs	2,269	31.6% (n=716)	0.28% (n=2)	68.40%	
no ROSC, initial unshockable rhythm, and unwitnessed by bystanders		Goto <sup>158</sup>	2013	Emergency Lifesaving Technicians	105,030	57.3% (n = 60,205)	0.7% (n = 73) one month survival with CPC 1-2	42.70%	

### 3.6 Summary of evidence

The majority of these validation studies considered only two individual CDRs. The first was developed by Verbeek, Marian, Vermeulen *et al* and was designed for BLS responders with AEDs, but subsequently validated against ALS providers as well (Table 3). This CDR recommends termination only where the arrest is not witnessed by EMS personnel, there was no defibrillation at any point during the arrest and there is no ROSC <sup>111</sup>. For reference, this will be known as the BLS CDR from hereon in. The second is the ALS CDR, again developed by Morrison, Verbeek, Marian *et al* <sup>112</sup>. This model takes the BLS criteria, but adds the requirements that the arrest was not witnessed by by-standers, and that there was no by-stander CPR (Table 4).

As can be seen in Table 3, the BLS CDR has been retrospectively validated ten times, and prospectively validated once. The numbers of patients in these studies varies greatly from 715 <sup>152</sup> to 151,152 <sup>153</sup>. The guideline has also been tested against a variety of practitioners, from BLS trained staff to Paramedics. All but one of the studies shows numbers of unexpected survivors following application of the guideline as under 1 percent, and transport rates vary between 25.1% <sup>153</sup> and 70.2% <sup>152</sup>.

The ALS CDR has been validated nine times (Table 4). All of these are retrospective studies. Many of the datasets are the same as those of the BLS TOR, resulting in a similar spread of patient numbers and grades of practitioner. For the ALS CDR transport rates vary between 65.8% <sup>155</sup> and 94% <sup>157</sup>.

Other than these BLS and ALS CDRs, four other CDRs were found to have been validated (Table 5). One of these supports on-scene termination where the patient is asystolic and the response time is greater than eight minutes <sup>110,149</sup>. This CDR will not be discussed further, as it so closely resembles the diagnosis of death available

to UK ambulance clinicians at the present time. As stated previously, the first stage of an assessment of a CDR is to establish that it is needed. From the perspective of a UK ambulance service that is able to terminate resuscitation attempts that result in asystole following 20 minutes of ALS, this guideline does not add clinical benefit.

Two CDRs were designed to identify patient survival with good neurologic function<sup>152, 158</sup>. The first allows for termination, provided the following criteria are met: The arrest was not witnessed by either a bystander or EMS personnel; the patient is aged 78 years or older; or asystole was the initial arrest rhythm. The number of patients identified for termination of efforts under this guideline were 5% (n=39). The used no ROSC, an initial non-shockable rhythm and unwitnessed arrest as its variable<sup>158</sup>. This model was retrospectively validated on a cohort of 105,030 patients. It recommended TOR for 57.3% (n=60,205) of these, and there were 0.7% (n=73) unexpected survivors with good neurologic outcomes.

The final model is based on response intervals, and is adjusted according to the patient's presenting rhythm (PEA or asystole), and in the case of PEA, whether this was witnessed or not<sup>156</sup>. This tool identified 54.6% (n=1,1315) potential TORs from a cohort of 20,705. There were 0.5% (n=57) survivors within this group.

The quality of these validations can be assessed utilising the criteria noted above. The need for a TOR CDR has been discussed at length in previous chapters, so needs no further clarification. In order to assess the rigor of the initial derivation of the BLS CDR, a previous paper was examined<sup>111</sup>. To identify the variables for the CDR the researchers used logistic regression analysis on a complete dataset of 662 patients. All variables are defined. It is of note that only 13 (<2%) survived to hospital discharge, which is low and may be indicative of the particular EMS system, or the

selected population in this study. The impact of this low survival rate on the derivation is difficult to assess. It was also identified that only five variables were used in the regression model. No rationale was given as to why other variables were not included.

Nevertheless, the CDR has been validated eleven times (varying both temporally and geographically), which suggests that despite any weaknesses in the derivation of the CDR, its results are reproducible to some extent. However, the marked variance in results, including one study for which unexpected survivors were greater than 1%, suggests that the CDR may not be universal. The BLS CDR is nevertheless the only TOR CDR to have been prospectively validated, though this was done by the same team that derived the guideline, which is not ideal.

The ALS CDR was derived by different, and arguably more robust methods<sup>128</sup>. The derivation study used a large database of 4673 patients, for which there was a 5.1% survival to discharge. Fifteen variables, including response intervals and initial cardiac rhythm were assessed for their associated with survival. Selection was initially made by adding a single variable to ROSC (the key predictor variable of interest, as established by previous research) and assessing the effect of the combination. The second variable was retained for the final regression model if changed the parameter estimate for ROSC by more than 10%.

Of note here is, the requirement that variables in a CDR should be adequately defined and reproducible<sup>143</sup>. The ALS CDR uses bystander CPR as a variable. As discussed in Chapter 2, CPR is effective when performed correctly. The inclusion of bystander CPR does not account for present, but ineffective CPR. This may



therefore reduce the number of potentially futile attempts being classified for termination.

Nine studies have sought to validate the ALS CDR. Again, all but one of these vary from the initial study both temporally and geographically. However, they suffer from the weakness that they are all retrospective studies. They also show a great difference in unexpected survivors (nil to 4.9%), which again suggests that the guideline may not be universal.

The remaining three guidelines do not benefit from large numbers of validation studies. The validation performed by Ruygrok, Byyny and Haukoos, and based on good neurological outcomes, used a CDR derived by Haukoos, Lewis and Niemann<sup>86</sup>. The derivation of this rule differs from those previously discussed, as it did not utilise a regression model. Rather, a form of binary recursive partitioning known as Classification and Regression Tree (CART) analysis was used. The disadvantage of this method is that the combined effects of variables may not be established. On the other hand, this method prevents the model being over-fitted. However, one of the variables is age greater than 78 years. Whilst this can be established from retrospective datasets in many cases, it is less certain that it can be established at the scene of an OHCA, particularly if relatives or carers are not present to provide information. The validation by Ruygrok was also limited due to the small geographical area used to collect data.

Skrifvars, Vayrynen, Kuisma et al validated the Helsinki 'do not attempt to resuscitate' guidelines, which were based on two studies by Vayrynen, Kuisma, Maatta, et al<sup>159, 160</sup>. The first of these considered the factors associated with short and long-term survival after asystolic out-of-hospital cardiac arrest, from a

prospectively gathered dataset of 1455 patients. They used both univariate and multivariate analysis to establish associations with survival. Although no CDR was created, the conclusion of the authors was that termination of resuscitation should be considered if the response interval was over 10 min or the ALS response time is over 10 –15 min in bystander-witnessed arrests. The Helsinki rule also includes the element that if ROSC cannot be achieved despite 20min of ALS, then the attempt should be terminated, which whilst widely accepted, was not part of this study.

The second element of the Helsinki guideline related to patients presenting with PEA. Again a study by Vayrynen et al was used as the basis for this element of the CDR. The study used logistic regression on 984 PEA arrests to establish associations with survival. As with the previously mentioned study, the study did not recommend a CDR, but concluded that prognosis is poor if the first response interval is over 15 min in bystander-witnessed arrests or if the duration of ALS exceeds 5.5 min in EMS-witnessed arrests. The Helsinki guideline uses this conclusion as a basis, but increases the second interval.

Despite its variation from the studies that derived it, the Helsinki guideline was validated by Skrifvars et al on a large prospectively gathered cohort of 12107 retrospective cases and found to be accurate at predicting survival with good neurologic outcomes, but less so for un-differentiated survival. However, whilst this dataset was temporally different to that of the derivation, it was geographically similar. It is also important to note that there was no data available to the researchers on how long resuscitation was attempted in cases where ROSC was not achieved. They therefore used the transport interval as a surrogate for this in their study, which may have influenced their results.

Goto, Maeda and Goto derived and validated their CDR<sup>158</sup>. The dataset of 495,607 patients was divided into two. They performed logistic regression analyses including 11 variables on one group to assess the association between them and one-month death or unfavourable neurological outcome. They validated the rule on the second group. The division was made by year, so there was a temporal difference between the two. It was noted, however, that the validation group had significantly higher one-month survival and one-month with good neurology rates than the derivation group (survival: 4.34% vs. 3.81%; good neurology: 2.04% vs. 1.60%; all  $P < 0.0001$ ). As well as a difference between the two, it is noted that these survival rates are low, suggesting that the rule may not be generalisable to locations with higher success rates.

### **3.7 Discussion**

As discussed in the previous chapters, the question of TOR in OHCA has both ethical implications and operational impacts on the ambulance service. A balance needs to be made between maximising the chance of a patient surviving from OHCA, and the unnecessary allocation of scarce ambulance resources for transporting futile resuscitation attempts to already over-stretched emergency departments, as well as the hazards such transport entails.

An important point to note, when comparing the various studies is the year from which they collected data. This is important, as the guidelines for resuscitation have undergone regular and significant changes over the years. In 1992, for example, the guidelines recommended that the ratio of compressions to ventilations should be 15:2, with compressions provided at 80 per minute, and to a depth of 4-5 cm<sup>161</sup>. In 1998 the recommended rate of compressions was increased to 100 per minute, and

it was recommended that if two rescuers were present, a ratio of five compressions to one ventilation should be adopted <sup>162</sup>. The guidelines from 2000 removed the variation for two responders, and recommended that the 15:2 ratio should be used no matter how many were in attendance <sup>163</sup>. The guidelines were revised again in 2005. These guidelines emphasised the importance of compressions, and recommended a ratio of thirty compressions to two ventilations as a result <sup>164</sup>. The guidelines introduced in 2010 placed even more emphasis on the importance of good compressions and recommended an increased rate of 100-120 a minute, to a depth of 5-6 cm <sup>165</sup>. The latest guidelines in 2015 did not adjust the recommendations on compressions <sup>27</sup>.

If one accepts the rationale of the latest guidelines that uninterrupted compressions are essential for improving outcomes, then arguably those studies that used data collected before 2010 were evaluating processes that were not maximising the potential for survival. Therefore it is questionable whether the results of earlier studies can safely be said to apply post 2010. Table 6 details each of the studies and indicates the guidelines that were used for each.

Study	Study period	Details of compressions
Cheong et al <sup>154</sup>	2010 - 2012	30:2 at 100 - 120 compressions per minute 5 – 6 cm
Chiang et al <sup>155</sup>	2008 - 2010	Potentially 30:2 at 100 compressions per minute 4 – 5 cm and 30:2 at 100 - 120 compressions per minute 5 – 6 cm
Goto et al <sup>158</sup>	2007 -2010	30:2 at 100 compressions per minute 4 – 5 cm
Kajino et al <sup>153</sup>	2005 - 2009	30:2 at 100 compressions per minute 4 – 5 cm
Morrison et al <sup>128</sup>	1998 -2003	Potentially 5:1 and 15:2 at 100 compressions per minute 4-5 cm,
Morrison et al <sup>147</sup>	2002 - 2004	15: 2 at 100 compressions per minute 4 – 5 cm
Morrison et al <sup>151</sup>	2006 - 2007	30:2 at 100 compressions per minute 4 – 5 cm
Ong et al <sup>110</sup>	1998 - 2003	Potentially 5:1 and 15:2 at 80 and 100 compressions per minute 4 – 5 cm
Ong et al <sup>149</sup>	2001 - 2004	15:2 at 100 compressions per minute 4 – 5 cm
Richman et al <sup>148</sup>	2004 - 2006	Potentially 15:2 and 30:2 at 100 compressions per minute 4 – 5 cm
Ruygrok et al <sup>152</sup>	2003 - 2004	15:2 at 100 compressions per minute 4 – 5 cm
Sasson et al <sup>150</sup>	2004 - 2006	Potentially 15:2 at 100 compressions per minute 4 – 5 cm, and 30:2 at 100 compressions per minute 4 – 5 cm
Skrifvars et al <sup>156</sup>	1990 - 2007	Potentially 5:1 at 80 compressions per minute 4 - 5 cm, and 15:2 at 80 and 100 compressions per minute 4 – 5 cm, and 30:2 at 100 compressions per minute 4 – 5 cm
Verhaert et al <sup>157</sup>	2008 - 2011	30:2 at 100 - 120 compressions per minute 5 – 6 cm

**Table 6 – Details of compressions from previous studies**

As well as differences in the resuscitation practice across the studies, it is apparent some variation also exists in relation to the reporting of the results of the studies. As predictive tests, TOR CDRs can be reported in one of two ways. Both would ideally have no survivors recommended for TOR, but how this is reported will vary depending on the approach. The first approach is to say that the test attempts to predict survival. In this case for the ideal test, which would recommend transport for all survivors, and both the sensitivity and the negative predictive value of the rule would be 100%. The alternative approach is an attempt to predict death. In this case

the CDR aims primarily to recommend TOR for all futile resuscitations. It would still ideally result in all survivors being transported, but from this viewpoint, the perfect test would have specificity and a positive predictive value of 100%. Of the validation studies considered, five used survival or survival with good neurologic outcome as the positive outcome<sup>110, 128, 149, 151, 152</sup> nine used death or poor neurologic outcome as the positive outcome<sup>147, 148, 150, 153-158</sup>. Morrison, Bigham, Kiss *et al* have considered the two reporting options and proposed that the standard reporting of CDRs for TOR should recommend TOR for patients who will not survive to hospital discharge, rather than seeking to identify potential survivors<sup>166</sup>. This is an important distinction, as a positive outcome from OHCA relies on a lot of factors out with the pre-hospital clinicians' control. Differences in ED staffing and capability, as well as ongoing care in intensive care units all play a part in a successful outcome. Therefore attempting to predict survival becomes difficult. Death however may be predicted earlier in the process and may be inevitable no matter what the ongoing care package consists of.

Morrison, Bigham, Kiss *et al* suggest that as death should be the predicted outcome, all such studies should report on the specificity (or true negative rate), which will identify the CDR's ability to identify potential survivors, and positive predictive value, which will demonstrate its recognition of futility. They also recommended that these studies should report the transport rate, as this is of particular operational importance to ambulance services. These recommendations are accepted as part of this thesis, as it is attempting to determine when the transport to ED of OHCA is futile and can therefore be terminated. It is not attempting to predict which patients would survive from an OHCA, though this group of patients will ideally be subject to transportation

as they do not fit the TOR criteria. This is the approach that will be adopted in later chapters.

It is worthy of note, however, that whilst Morrison, Bigham, Kiss *et al* do not dwell on the importance of sensitivity (or true positive rate) in their paper, it is proposed here that it is of great importance. Whilst it is accepted that any CDR will result in patients being transported who ultimately die, it is important that there are as few of these cases as possible. When death is considered the positive outcome and the objective of the CDR is to limit the number of futile transports, then the sensitivity of the CDR will indicate how well that test recognises futility. Although it is important that the test should identify potential survivors, it should also minimise the number of futile transports to hospital. If one does not interrogate the sensitivity of a test, there is the potential that the rule recognises potential survivors, but at the cost of transporting undue numbers of futile attempts to hospital. By requiring the transport of greater numbers to ED, any CDR will inevitably capture more survivors. However, this alone does not maximise the identification of futile transport, and the ethical and operational burden that these entail. Sensitivity is an indicator of how well a TOR CDR captures these futile attempts. The aim of any TOR CDR should be to identify as many patients as possible, who would not benefit from continued resuscitation and transport, whilst allowing potential survivors the benefit of continued attempts. Inevitably, some of those identified for transport will not survive, and perhaps some of those identified for termination may be potential survivors, but unless the subset of transported non-survivors is reduced as much as possible, then the CDR is not achieving its maximum benefit.

As well as the differences in statistical approach, there are other confounding factors, which prevent the results of the reviewed studies being compared directly.

Of the fourteen studies found, five were concerned with survival with good neurological outcome. Another study had good neurological outcome as a primary outcome, but also looked at survival as a secondary outcome<sup>154</sup>. All others considered only survival, irrespective of neurological outcome. The results of the former cannot therefore be compared directly with those of the latter.

There are also differences in the patient cohort within the various studies. In the studies conducted by Morrison<sup>147</sup>, Richman<sup>148</sup>, Ong<sup>110,149</sup>, Kajino<sup>153</sup> Chiang<sup>155</sup> and Cheong<sup>154</sup> the EMS systems did not have any existing TOR guidelines in place at the time the data was collected. This means that that all OHCA patients were included in the study. This would include patients in an asystolic rhythm at the time the transport decision was made. Although the EMS system studied by Verhaerta<sup>157</sup> did have the ability to terminate patients on scene, the design of the study was such that all patients, whether terminated on scene or not, were included for analysis. The study by Skrifvars<sup>167</sup> was conducted in an EMS system that allowed for termination in cases of ongoing asystole despite 30 minutes of resuscitation. It is unclear whether these patients were included in the statistics for the study. However, this study included only those patients presenting with either asystole or PEA as an initial rhythm and included patients with an arrest of non-cardiac aetiology (excluding patients with either drowning or trauma). In two studies (Morrison<sup>151</sup> and Ruygrok<sup>152</sup>) it appears that pre-hospital clinicians were able to apply existing CDRs at the time of the studies, in order to terminate resuscitation attempts, and that these patients were included in the statistics.

In UK ambulance trusts, paramedics may already terminate resuscitation attempts following twenty minutes of ALS, where the patient is asystolic<sup>68</sup>. Including this subset of patients in a TOR study produces exaggerated results for a CDR predicting



death, when compared with systems using such a rule, as the consensus is that these patients have a negligible chance of survival. By contrast, excluding this subset of patients from a study means that the proportion of unexpected survivors as a denominator of those expected to die is likely to increase.

The type and training of responders varied across the studies as well (BLS with AED<sup>147,110,149</sup>, emergency life technicians<sup>153</sup>, ILS paramedic<sup>154</sup>, ALS paramedic<sup>112,157</sup>, and multi-tiered responses<sup>148, 151, 152, 155</sup>). This may have had an effect on the survival of patients in each group, which may therefore prevent the results being generalised across other pre-hospital systems.

All but one of the validation studies that were reviewed reported survival rates following a positive TOR that were within the accepted definition of futility (ranging from zero to 0.51%) and so all appear to be able to identify futile transportation to hospital. However, the study by Chiang, Ko, Chang *et al* retrospectively validated both the BLS and ALS CDRs and found that 1.9–4.9% of patients who survived were misclassified as non-survivors<sup>155</sup>. The authors suggest two possible reasons for this. Firstly, the high number and density of tertiary hospitals in Taipei may have had an influence on the increased numbers of survivors. Secondly, they suggest there may have been selection bias within their study cohort. They report anecdotally that some families refused transport of the patient if the patient was either old or was bedridden. This may have led to a reduction of TOR-positive non-survivors. However, they go on to say that even if all 1534 of these cases were added to as TOR-positive, the number of unexpected survivors was still higher than 1%. This is important, as it emphasises that TOR CDRs need to be validated in the population to which they are to be applied, as variances in response model, treatment options or population may have an impact on their application. That a CDR has been validated

in one healthcare system does not automatically validate it in terms of all other healthcare systems.

There is perhaps an expectation that as the number of false positive terminations (unexpected survivors) approaches zero, the frequency of recommended transport increases. Unless the sensitivity of a CDR is high, then this will necessarily be the case. By reducing the number of patients who are potentially TOR-positive and thereby transporting greater numbers to hospital, one would anticipate the number of unexpected survivors to decrease, at a cost of transporting more futile attempts. However, if the CDR has higher sensitivity, then a reduction in the number of false positives should be achieved without an increase in transportation. There has been extensive study of both the BLS CDR criteria and the ALS CDR criteria and they have both been shown to identify correctly those patients who will not benefit by transportation to hospital. However, transport rates using both CDRs have been shown to vary considerably between systems and populations. The BLS CDR has shown transport rates of 25.1% to 70.2% and the ALS TOR 65.8% to 94%. The lowest transport rate for the ALS CDR found in this review was recorded by a study looking at good neurological outcomes, so the outcomes cannot be compared with other studies. However, the lowest reported transport rate over all used the BLS CDR as a decision tool, and reported transportation rates of only 25.1% <sup>153</sup>. However, this study was based in Japan, where no existing TOR guideline exists. This means that these results also capture resuscitations that would be terminated following current 'asystole guidelines' present in the UK. As noted previously, this may artificially reduce the numbers of transports, when compared with systems that already exclude this group of patients under existing TOR CDRs. On the data provided, the effects of removing this cohort of patients from the final figures could

not be achieved. Therefore the results of the CDR on only those patients not already captured by the 'asystole guidelines' could not be established. The highest reported transport rate among these studies was 94.5%, and again measured good neurology as an outcome <sup>168</sup>. This guideline resulted in only 5.5% of patients proving TOR positive and was the most restrictive in terms of criteria for TOR. Nevertheless the highest transport rate measuring survival was for the ALS CDR (94%)<sup>157</sup>.

The proportion of patients transported to hospital is of particular importance to ambulance operations, as it is this figure that determines the operational impact on the service, as opposed to the clinical impact of the CDR. Nevertheless, a TOR CDR, however promising both clinically and operationally, is limited in its application if the validation process used is low level. In order for a prognostic tool to be implemented into clinical practice, it needs to be validated in such a way that it, that it is shown to work satisfactorily for patients other than those from whose data it was derived <sup>145</sup>.

All but one of these validations are of level four, as defined by McGinn, *et al* <sup>141</sup>. The only validation which is level two, and therefore robust enough to be implemented, was tested only in an environment where responders were BLS and AED trained<sup>147</sup>. This view is supported by Sherbino, whose appraisal of available literature in 2010 concluded that "In the setting of OHCA receiving exclusive basic life support with AED, only the BLS-TOR rule has been prospectively validated in a rigorous fashion to warrant widespread use" (p84)<sup>146</sup>. Although subsequent validation suggests the BLS-TOR guideline may be applicable to ALS scenarios<sup>112</sup>, this was only validated as a level four retrospective study. A second study collected data prospectively, but the CDR was applied retrospectively, rather than by the attending clinicians, and so this is also a retrospective validation <sup>151</sup>.

As already noted, it is important to recognise that the BLS and ALS CDRs are designed to be applied to all adult cardiac arrests of cardiac aetiology. By contrast, the Trust already employs a TOR CDR. This allows for TOR where ALS results in asystole after twenty minutes of ALS, and is irrespective of any presenting rhythm, rhythm changes throughout the arrest, or involvement of by-standers. Any TOR CDR derived using patients within the area of the Trust will therefore apply only to those patients who do not fulfil the criteria presently in use, and who are consequently transported to hospital. So any patient fulfilling the present TOR criteria will not be included in the analysis. Therefore, excluded from the patient group will be any patient whose resuscitation attempt results in asystole. Those currently taken to hospital by the Trust will therefore be those patients who have either a PEA or a persistent VF/ pVT rhythm, following ALS.

As with any literature review, this study may be limited by the factors inherent to any such search, including publication and selection bias. In particular, language restrictions prevented the inclusion of non-English language studies when searching the clinical databases. Another limitation is that the search strategy used and ensuing manual screening may have been fallible and some relevant studies may have been omitted. However, all due care was taken to ensure that the impact of this was reduced as much as possible. Moreover, the search terms were retained and alerts enabled, so that articles published subsequently could still be reviewed and included here, when appropriate.

### **3.8 The need for further research**

Girija, Sudha, Cauvery *et al* have discussed the efficacy of partaking in new research<sup>169</sup>. Although concerned with the social sciences, their suggested requirements are equally fitting to health research. They maintain that research should be novel, and

even if touched by other research, must be an area in need of further investigation. As evidenced from the review of the literature, there are thirteen published reports, which purport to validate TOR CDRs. However, only one of these is anything other than a data-based retrospective study, and that was validated in a pre-hospital system utilising BLS with AEDs, unlike the ALS system used in the UK. Moreover, none of the studies were conducted under the current guidelines for resuscitation, and the majority were assessed in pre-hospital systems that did not have the existing termination rules that are available to UK ambulance Trusts. All of this means that the results cannot be generalised to the population of patients of interest to this thesis. Certainly there is a paucity of evidence to support change without further study.

This view is supported by the Resuscitation Council (UK), who in their latest guidelines, state that “The decision about when to stop a cardiac arrest where pulseless electrical activity (PEA) persists is less clear and is not currently within the UK Ambulance Service Clinical Practice Guidelines (2013)...There is limited evidence to support when one should terminate a PEA cardiac arrest...”<sup>170</sup>. This highlights the need for more research aimed specifically at the patient group of interest. Without further research to establish whether and when PEA rhythms are futile, then this group of patients will continue to be transported to hospital.

Girija, Sudha, Cauvery et al go on to suggest that research should be up to date and relevant, and should come out with pragmatic solutions to the issue. It has been shown in previous chapters that the majority of resuscitation attempts that are transported to hospital do not result in the patient’s survival, despite the existence of TOR guidelines for asystolic patients, which already reduce the number of patients who undergo transport. It has also been shown that there is support for the position

that futile medical interventions are unethical. This literature review has shown that there are nevertheless tools available to establish when a resuscitation attempt should be terminated, due to its futility, but that none of these tools were either derived or validated in a pre-hospital system similar to that of the UK Trust in question. Nor were they designed to complement the present TOR guidelines currently in place in the Trust. Research is needed to establish whether a similar tool can be derived and validated for the population served by the Trust, or if the previously validated TOR CDRs are appropriate for identifying patients presently transported and for who transport to hospital is futile. The introduction of such a tool would potentially reduce the number of adult OHCA patients transported to hospital, and the risks associated with that transport, whilst still protecting those patients for who continued efforts may be successful. Not only could such a tool address the ethical issues of futile treatment for the appropriate patients, but may also benefit the wider health economy, due to the resulting increase in available resources to attend and treat other patients both in the pre-hospital environment and within hospitals.

## 4. Chapter Four – Methodology and methods

### 4.1 Qualitative vs quantitative

In the previous chapter, it was concluded that whilst various CDRs have been derived for TOR, the CDRs do not necessarily produce similar results across different populations and pre-hospital systems, and the existing research is not robust enough to consider changing the practice in a UK ambulance Trust when critiqued using the criteria defined by McGinn, Guyatt, Wyer *et al* <sup>141</sup>. Furthermore, the populations used to validate these existing CDRs are different from those relevant to the Trust, as they include those patients already suitable for termination under existing rules available for the termination of asystolic rhythms. Therefore, having established the need for further research, this chapter will discuss the various methodologies available to researchers and propose the most appropriate one for this project. It will then give an overview of the methods used in subsequent chapters to gather and analyse data.

Methodology may be defined as the general principle or approach that guides a research project<sup>171</sup>. In its broadest terms all research is the search for new knowledge. However, in order to be able to inform future practice, it must be performed in a way that allows others to follow the methods and assess the robustness of its results <sup>172</sup>. Research methodology provides the structure for research. A methodology provides the overall approach to the research and offers a framework for answering questions as to constraints, dilemmas and ethical choices that may present themselves <sup>171</sup>. There are different ways to classify research, and one of the most common classifications is into either qualitative or quantitative research. The former, which is often, though not exclusively, associated with the social sciences, explores experiences, behaviour and attitudes through methods

such as focus groups, interviews or facilitation. Qualitative research does not aim to produce quantifiable answers to a particular research question, but rather seeks to produce insights on social interactions <sup>173</sup>. The methods employed by qualitative research tend to focus on fewer participants, but the contact interval with them is usually longer. The precise methods used will depend on the exact methodology chosen for the research and there is no single approach <sup>174</sup>. So, for example, ethnography, which evolved from the study of anthropology, may rely heavily on fieldwork, where the researcher participates in a group's activities and observes its interactions and behaviour. By contrast, action research works with a closed group of participants and aims to facilitate change by working through defined stages of planning, acting, observing and reflecting. Grounded theory is another qualitative methodology, which allows a theory to emerge from gathered data. Through a series of interviews or focus groups, grounded theory gathers information from an unspecified number of participants, until such time as no new information is being obtained. Once this point of saturation is reached, a theory or idea may emerge, which was previously unconsidered.

Quantitative methodology is more associated with the natural sciences, and differs from qualitative in that it is concerned primarily with statistics, gathered using a variety of means and depending on the methods chosen. One of the tenants of quantitative methodology is that it is objective and value-free in its investigation of a material reality <sup>175</sup>. This has its basis in the theories of positivism, which purports that scientific statements are based only upon empirical observations, and the logical inferences based on them <sup>176</sup>. Although this is an over-simplified view of the methodology, it does emphasise the difference in approach to qualitative study.



Nevertheless, this view of the scientific approach has been criticised in recent years; not least by Stephen Hawking, who notes that;

“Up until now, most scientists have been too occupied with the development of new theories that describe what the universe is to ask the question why” (pp174) <sup>177</sup>.

Despite the apparent dichotomy between the two methodologies, it is possible to conduct mixed-methods studies. These studies will have different methods of data collection that include qualitative data such as surveys, combined with qualitative data such as interviews. The relative merits and shortcomings of the different methodologies are beyond the scope of this thesis. However, to determine which methodology to use for this research, it was necessary to focus on the aim of the thesis. For example, if the focus was on the decision-making process relating to termination of resuscitation, then a grounded approach would allow one to develop theories from the ideas and experiences of clinicians who have experienced this, by means of interviews or focus groups. Similarly, an ethnographical approach would allow for observations in the field to establish how decisions were made by different levels of clinician when presented with difficult decisions about termination of resuscitation. Although these approaches would certainly add to the knowledge of decision-making in the field, the aim of this thesis is to determine whether there are key objective determinants, which can be used to classify a resuscitation attempt as futile, and which would otherwise result in transport. Some of the motivations behind this research do have qualitative features; such as the effect on clinicians and family member when they are required to continue resuscitation on patients for whom they believe their efforts are futile. However, the primary aim was to produce evidence, which could be used to change current practice. Qualitative studies, along with descriptive studies, opinion leaders and patient preference are all valid tools in

modern evidence-based practice<sup>178</sup>. Nevertheless, as the previous chapter showed, in other pre-hospital emergency systems and populations, it has been possible to determine objectively when a resuscitation attempt is likely to prove futile. This was done by obtaining objective data on cardiac arrests and analysing it using statistical methods to determine which independent factors were associated with poor outcomes. This approach directed the study firmly towards a quantitative methodology.

## **4.2 Methods**

Having established that this research would follow a quantitative methodology, a research design was required to answer the research question. This section gives an overview of the methods used in subsequent chapters. It provides an understanding of why certain methods were used. More detail on the decisions made at each stage of the study is provided in following chapters.

The second objective of this thesis, given in chapter two was:

To derive a TOR CDR for adult OHCA of cardiac aetiology that is appropriate for use by pre-hospital clinicians, and which reduces the number of futile resuscitation attempts transported to hospital.

The third and fourth objectives were to validate this rule, first retrospectively and then prospectively. This then led to the hypothesis that there are objective characteristics that can determine when an adult patient suffering an OHCA of cardiac cause will not survive a cardiac arrest despite ongoing resuscitation attempts and transport to ED. This is a causal hypothesis, as it not only describes a relationship between two or more variables, but also implies that a change in one of those variables will lead to changes in the other<sup>175</sup>. By generating this hypothesis it was now possible to aim to

design a study that would lead to predictions based on observation, and in particular towards the outcome of resuscitation attempts. In deciding how to design this study, it was important to consider generalisation. Generalisation is the concept that results will be applicable to situations similar to those studied. The notion of generalisation has led to several commentators developing hierarchies of evidence <sup>139, 179</sup>, as discussed in chapter three. The hierarchies are used to show the increasing risk of bias, and reduced generalisation that results from different research designs. Although these hierarchies vary, they are generally consistent in that they rate systematic reviews or meta-analysis of randomised controlled trials as the 'gold standard' of primary research <sup>180</sup>. Next are randomised controlled trials (RCTs), which allow for rigorous evaluation of a single variable and are designed to eradicate bias by comparing identical groups <sup>181</sup>. However, the complexity of resuscitation practice and the posed clinical question make an RCT impractical due to the number of influencing variables. Even if possible, an RCT would raise ethical issues about randomising patients for resuscitation that would be difficult, if not impossible to justify. Furthermore, one could not randomly terminate a resuscitation attempt at scene and determine whether that patient would survive to hospital discharge due to clinical equipoise.

Therefore, the components of the TOR CDR were established by performing a retrospective cohort study using OHCA data collected by the Trust. This data was refined to include only those adult patients who presented with an OHCA of presumed cardiac aetiology, and who were transported to hospital. Cohort studies are a 'nonexperimental' research design, as participants are not allocated randomly. They are therefore ranked lower in the hierarchy of evidence than RCTs. They do,

however, provide evidence of the factors influencing outcomes and in population studies they are the only type of study that can accurately identify risk factors <sup>182</sup>.

The aim was to review the variables collected by a single ambulance trust on all pre-hospital cardiac arrests and determine whether certain variables were associated with and predictive of death for adult OHCA of presumed cardiac aetiology. In this way, statistical methods were used to develop a model that would predict future observations. It was decided that an initial retrospective study could be validated prospectively, once the model had been developed and refined if necessary. This approach was considered to be important to improve the rigour of the CDR. As Altman and Royston have argued; a statistically validated model, which passes all the appropriate statistical tests, has no clinical value unless it can be shown successfully to predict outcome <sup>145</sup>. In order to do this the performance of a model must be tested using data other than that used for the model development, and ideally in a clinical setting.

### **4.3 Population**

The data for this study were taken from a large United Kingdom Ambulance Trust (the Trust), covering both large urban centres and remote rural areas. The Trust covers a geographical area of approximately 5,400 square miles, with a population of approximately seven million people. The Trust responds to over one million medical incidents per year. It operates approximately 700 response vehicles, being a mixture of single crewed rapid response cars and double crewed ambulances. It has a combined technician (BLS) and paramedic (ALS) staff, with some crews being exclusively one or the other, whilst other crews are mixed. This variation is the result of rostering practicalities, and local requirements, rather than universal design. The Trust also utilises a system of community first responders, who respond via pager to

a number of incidents, including adult OHCA and who are equipped with AEDs. The Trust supports a scheme of public access defibrillators, which allows for by-standers to collect an AED, if it is within a reasonable distance of the scene. The Trust currently operates a TOR guideline, in line with the majority of UK ambulance services, which allows for termination only if, following 20 minutes of ALS, the patient is in an asystolic rhythm. Therefore, whilst BLS staff may occasionally be the only attending response to an arrest, only ALS responders are permitted to terminate an arrest attempt. Ambulance clinicians of all grades are also not required to initiate CPR where there are obvious signs of death, or where there has been no effective BLS for more than fifteen minutes since collapse, and the patient is in an asystolic rhythm.

#### **4.4 Study design**

Having decided on an initial retrospective cohort study, there was a need to determine which statistical model to use for this. There is a variety of opinion on which statistical model to use for different tasks, and much of that opinion is based on personal preference of the researcher, rather than any hard and fast rules <sup>183</sup>.

Lehmann quotes A. P. Dawid as saying:

“In general, the theoretician is happy to accept that his abstract probability triple  $(\Omega, \mathcal{A}, P)$  was found under a gooseberry bush, while the applied statistician’s model ‘just grewed’.” <sup>184</sup>

As the aim was to predict an outcome variable from several predictor variables, multiple regression was chosen as the tool. However, linear regression assumes linear relationships between variables. When the dependent variable is categorical this assumption is violated. The dependent variable for this study was dichotomous: death vs survival to hospital discharge (survival), so binominal logistic regression

was chosen to overcome this problem of violating the linearity assumption. Binomial logistic regression enables one to predict the likelihood that a subject will fall into one of two possible outcomes, given a set of dependent variables. Binomial logistic regression (often called simply logistic regression) models a relationship between multiple independent variables and a single dependent variable. However, a transformation is applied so rather than directly predicting the category of the binomial logistic regression, the logit of the dependent variable is predicted. This makes the form of the relationship between independent and dependent variables linear, but leaves the relationship itself non-linear. To do this, the logistic regression model first takes the odds of the dependent variable happening following variations to each independent variable. It then takes the ratio of those odds and then the logarithm of that ratio in order to transform the dependent variable into a continuous criterion. So, whilst the dependent variable is binomial, the regression is conducted on the logit, which is the continuous criterion <sup>185</sup>. The predicted value of the logit is then converted back into predicted odds using the inverse of the logarithm. Therefore, whilst the observed dependent variable in logistic regression is dichotomous, logistic regression is able to estimate the odds as a continuous variable. Categorical prediction can then be based on the computed odds of a success.

For example, if four independent variables are "X1 to X4" and the probability of the dependent variable is "Y", binomial logistic regression produces the model:

$$P(Y) = 1 / (1 + e^{-(\beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_4 X_4 + \epsilon_i)})$$

Where  $\beta_0$  is the constant,  $\beta_1$ ,  $\beta_2$ ,  $\beta_3$ , and  $\beta_4$  are the coefficients for  $X_1$ ,  $X_2$ ,  $X_3$ , and  $X_4$  respectively and  $\epsilon$  is a residual term <sup>186</sup>. A point to note here is that the relationship

between any independent variable and the dependent variable depends on the values of the other variables in the model. So, for example, in a simple model with age and sex as independent variables, the sex (male/female) is different across ages. It must also be noted that as with all statistical modelling, there are inherent dangers, such as the model being over fitted, resulting in false positive associations, or predictions that are too extreme, so results must be viewed with caution. As one of the great statisticians, George Box commented “All models are wrong, but some are useful” <sup>187</sup>. This was borne in mind as variables were selected for inclusion at each stage of the CDR development.

This process was applied in three stages. First, all potential variables were assessed for their association with the outcome (survival). Arguably, by doing this there was the potential of excluding the possibility of detecting the effect of small combined differences across the factors <sup>183</sup>. However, it was decided that at this stage the effects of small combined differences could be sacrificed in order to produce a simplified CDR, which would be applicable in the field. Having established which independent variables may be associated with outcomes for pre-hospital cardiac arrest, a decision was taken not to include certain variables into the subsequent calculations to determine the CDR. This was done by excluding those variables which could be excluded on ethical grounds, as well as those that could not be established with any degree of certainty by clinicians at the scene of an arrest. As it is ambulance clinicians who would be expected to implement the CDR, only variables that could be established with accuracy on scene were considered for further analysis. This would ensure that the CDR was clinically applicable, rather than being a purely academic exercise. The remaining variables were then included in the regression model. The final selection of variables to include in the CDR was

then considered. Full details of that process are explained in detail in chapter 5, and include the selection of variables to be included in the regression process and how these were refined for inclusion in the CDR.

Whilst there are inherent statistical tests that attempt to measure how well the model fits the data, such as the Nagelkerke  $R^2$ , it was decided early on that the model would be validated as cohort studies against subsequent data sets of actual cardiac arrest events. In this way, there is some assurance of generalisability of the CDR that had been created from the original data set. It was decided that both retrospective and prospective cohort studies would be used as the methods for validation. This would satisfy McGinn's requirements for implementing a CDR into clinical practice <sup>141</sup>. The retrospective validation was chosen as it could utilise data already gathered by the Trust. This would provide a substantial data set, without the requirement for data gathering from the Trust's clinicians. Any problems identified at this stage could then be rectified easily. The second, prospective cohort study required significant operational input from the Trust's clinicians, which is described in detail in chapter 7.

Both the retrospective and prospective cohort studies aimed to determine sensitivity and positive predictive value of the established decision rule, as well as the specificity and negative predictive values. These values are determined, as with other diagnostic tests, by reporting the results using a 2×2 diagnostic test results table (Table 7). It is important to note here that as the rule is aiming to determine futile resuscitations, the positive outcome is death. This will be discussed further in later chapters.



<b>TOR Guideline</b>	<b>Died</b>	<b>Survived</b>	<b>Total</b>
<b>Terminate</b>	a	b	a+b
<b>Transport</b>	c	d	c+d
<b>Total</b>	a+c	b+d	a+b+c+d

**Table 7 – 2x2 table of results**

The 2x2 table identifies the following subsets of patients:

- (a) True positives, which are those patients for whom the rule predicted death and did in fact die;
- (b) False positives, where the rule predicted death, but the patient survived;
- (c) False negatives, where the rule predicted survival but the patient died;
- (d) True negatives, where the rule predicted survival and the patient survived.

From these results, one can determine the sensitivity and specificity of the test. The sensitivity of a test denotes its ability to identify correctly those patients whose resuscitation should be terminated due to the futility of onward transport (as the CDR is designed to determine futile attempts, rather than survival). This is established by the equation:

$$\text{Sensitivity} = \text{True positives} / (\text{True positives} + \text{False negatives})$$

The specificity of this test refers to its ability to identify those patients who should be transported (due to not fulfilling the criteria of the termination rule) and who go on to survive. This is established by the equation:

$$\text{Specificity} = \text{True negatives} / (\text{True negatives} + \text{False positives})$$

One can also use these results to establish the positive predictive value (PPV) of the test. That is, how likely it is at a patient will not survive, when the rule recommends

termination. As such, PPV has more real world meaning than sensitivity or specificity. It is established by the equation:

$$\text{Positive Predictive Value} = \text{True positives} / (\text{True positives} + \text{False positives})$$

The negative predictive value (NPV) determines how likely it is that a patient will survive when the decision rule recommends transport. This is established by the equation:

$$\text{Negative Predictive Value} = \text{True negatives} / (\text{True negatives} + \text{False negatives})$$

Although the number of expected survivors in any population of OHCA patients is likely to be low, the NPV is a good indicator for the effectiveness of any CDR that is produced. Although not designed to determine survivors, a high NPV would indicate that fewer futile attempts have been classified as survivable. A high PPV, on the other hand, will indicate that there are few unexpected survivors in the group predicted to die, which is also a good indicator of an effective CDR in these circumstances.

It was apparent that in order to justify the development of a new CDR, it should be compared against those already validated: the BLS and ALS CDRs discussed previously. Therefore at each stage of the process, both of these CDRs were applied to the patient population and evaluated against the TOR CDR that had been derived. As any effective TOR CDR would require the number of false negatives (unexpected survivors) to be less than 1%, a high specificity (ideally 100%) was expected for all three of the CDRs. This would indicate that fewer potential survivors were classified in the futile group of OHCA patients. Therefore it was predicted that the specificity of the three CDRs would be broadly similar – they should all recommend transport for potential survivors. On the other hand, whilst the test is aimed to identify futile

resuscitations, it is not expected that sensitivity will be as high in any of the CDRs. This is because there were still expected to be a number of patients transported to hospital, who do not survive (false negatives). By assessing the comparative sensitivity of the three CDRs, their ability to predict death was established.

The result of a higher sensitivity will be fewer futile resuscitations being transported to hospital. As discussed earlier, if the only goal is to identify potential survivors, then transporting all OHCA patients to hospital would achieve this. However, this does not alleviate the issues of finite resources or the ethical dilemma of continuing resuscitation attempts when they are ultimately futile. Therefore all decisions relating to TOR must balance the need to reduce unexpected survivors to an acceptable number, but at the same time minimise the number of futile transports. A comparison of the sensitivity of each rule addresses this latter point.

Furthermore, the efficacy of the three CDRs was also assessed by means of their receiver operating characteristic (ROC). The ROC space is a graph, which plots the performance of a binary classifier system by plotting the true positive rate (sensitivity) on the y axis against the false-positive rate (calculated as  $1 - \text{specificity}$ ) on the x axis. Analysis of the ROC space helps to identify possibly optimal models. The optimum prediction method (also called a perfect classification) would result in a point in the top left corner of the ROC space, which represents 100% sensitivity (no false negatives) and 100% specificity (no false positives). A diagonal line divides the ROC space. A point above this line indicates a result that is better than random, whereas a point below the line indicates a worse than random result.

## 4.5 Cost savings

The final element of this research involves an estimate of cost savings following the introduction of the TOR CDR. Although the concept of futility is heavily bound with issues of ethics, as previously discussed, there are also distinct economic factors, which need to be considered. As emphasised in previous chapters, all resources in terms of pre-hospital and ED staff, time and facilities are limited, and increasingly under pressure, both due to economics and capacity. Increasingly, there are pressures within the NHS to reduce cost, whilst maintaining efficiency. The NHS Five Year Forward View emphasised the need to drive efficiency in order to maximise resources<sup>188</sup>. This document emphasised that with no additional annual efficiencies, and flat real terms funding, the continued growth in demand on NHS resources could produce a deficit of almost £30 billion a year by 2020/21. It highlighted an ambition for the NHS to attain 2% net efficiency gains each year for the rest of the decade, and the possibility that this could increase to 3% over time. This was supported by the Association of Ambulance Chief Executives, whose vision for the future of the ambulance service acknowledged the need for financial savings, whilst maintaining patient care<sup>189</sup>. Although this latter document was aimed primarily at urgent, rather than emergency care provision, its underlying message is that too many patients are transported to ED, when other options may be available to ambulance clinicians. It suggests that reducing transportation plays a pivotal role in improving cost efficiencies. Similarly, the National Institute for Health Research discussed the cost-effectiveness of ambulance service practices<sup>190</sup>. Although this paper considered OHCA, it did not comment on the appropriateness of transportation, but rather at interventions on scene. Nevertheless, it emphasised throughout the need for ambulance clinicians to deliver care solutions on scene, when appropriate, as

opposed to transporting patients to hospital. The NHS Confederation have also stressed that whilst emergency care pressures are most visible in the emergency department, they result from systemic issues, including those of the ambulance service <sup>191</sup>. They emphasised that reducing avoidable emergency admissions is one of the key issues in reducing unnecessary cost. Therefore, in order to understand the impact of any proposed CDR, it is important to understand the economic impact they will have on healthcare system as a whole.

The characteristics that define an economic analysis are a comparison of choices and the relative costs and consequences of those competing choices. However, there is no standard method of economic evaluation. An economic analysis may take different forms, depending on the measurements, costs and consequences that are considered. Therefore the choice of method used depends on the answer to two questions. Firstly, whether there are comparisons being made between two or more alternative options, and secondly, whether both costs and consequences are being compared. If one examines both the costs and consequences of two or more alternatives, then this is considered to be a full economic evaluation. Within this group of methods, there are three potential techniques that can be employed. For example, if one was comparing different interventions, but measuring a common effect, which may vary between the two, then a cost-effectiveness analysis may be undertaken. A cost-utility analysis takes a broader measure of benefit and makes adjustments for quality of life, whilst providing comparisons of a generic outcome measure. A third method, the cost-benefit analysis, translates the various components of an effect (e.g. quality-adjusted life-years (QALYs) gained, complications or disability days avoided) into a monetary value and seeks to establish the net benefit or loss of one option over another. Other forms of economic

analysis are available, which do not necessarily consider all the elements required for a full economic evaluation. Drummond, Sculpher, Torrance *et al* consider these partial evaluation techniques, which may not consider two or more alternatives, or which may not examine both the costs and consequences of the examined alternatives <sup>192</sup>.

There are difficulties in applying a full economic evaluation to the application of a TOR CDR. First and foremost, the CDR is not designed to affect patient outcomes. Rather, a TOR CDR aims to identify patients who will not survive, and to allow termination on scene. The outcome for the individual patient does not change. Potential benefits of reducing the number of futile transportations can be anticipated. However, these do not relate to the individual patient being transported. Rather they are implicit benefits. They include the availability of both ambulance and hospital resources that could otherwise be utilised, if not allocated to an ultimately futile resuscitation attempt. For the ambulance resource, this could include their availability for other emergency incidents. In-hospital benefits could include the availability of clinical staff to attend other patients, and the availability of beds to accommodate other patients. These benefits, although real, cannot easily be quantified.

The approach taken was therefore to determine the cost savings of implementing the CDR from an acute care perspective. This was done by reviewing the possible locations at which a futile resuscitation attempt could be terminated. The cost of each alternative was made on the basis of assumptions, which will be discussed further in Chapter 8. However, it is important to note that these assumptions were made on the basis that they deliberately under-estimated the full costs. This was done so as not to over-emphasise any financial benefits of implementing a CDR. The

data from phase 3 were used to calculate the costs. The costs were established for the current situation, where all patients are transported, and repeated for the TOR CDR, as well as the BLS CDR and ALS CDR. From this, the cost savings were compared.

#### **4.6 Approval and ethics**

Before this study was initiated, approval was sought to ensure the methodology was appropriate for the study; the methods selected were valid and that the participants were appropriately safeguarded. Approval was sought from three organisations, due to the nature of the study. A proposal was presented to Northumbria University for academic approval and a subsequent application was made to and approved by the Faculty Ethics Review Panel. As the research was to be conducted using data, patients and personnel from a UK Ambulance Trust, a submission was also made to and approved by the Trust's Research and Development team. As the study required the creation and maintenance of a database relating to OHCA, approval was also sought and approved by the National Health Service Health Research Authority (Appendix 4).

#### **4.7 Conclusion**

In this chapter methodology and methods employed in subsequent chapters were discussed. The use of a quantitative methodology has been justified and then an overview of the methods employed to establish and validate the TOR CDR were given. The following chapters will look in turn at the derivation of the CDR and then its validation, both retrospectively and prospectively. Finally the cost savings will be discussed in detail. Each of these chapters will discuss in more detail the methods relevant to that chapter.

## **5. Chapter Five - Derivation of a clinical decision rule (Phase 1)**

In previous chapters a definition of futility has been established and it has been confirmed that TOR CDRs may be able to predict those adult OHCA of cardiac aetiology that will not have a successful outcome, despite transport to hospital. In this chapter, phase 1 of the study will be discussed. This phase addresses the second objective of the thesis: To derive a TOR CDR for adult OHCA of cardiac aetiology that is appropriate for use by pre-hospital clinicians. Therefore the aim was to develop a TOR CDR that could be used by pre-hospital clinicians to determine when a resuscitation attempt that is currently transported to hospital under existing guidelines could safely be terminated at scene, without the need for transport. The creation of such a CDR required the identification of certain characteristics, or combination of characteristics, which could be used to identify futile resuscitation attempts that under current practice would result in transportation of the patient.

Since 1991, the “Utstein style” of defining and reporting on out-of-hospital resuscitation has been internationally accepted. This consensus, reached following an international multidisciplinary meeting held at the Utstein Abbey, Norway, in June 1990 was aimed at providing uniformity in reporting OHCA and resuscitation attempts<sup>193</sup>. The Utstein templates have subsequently been updated, with the latest version announced in 2014<sup>194</sup>. Wherever possible, the Utstein definitions are used throughout this and subsequent chapters. However, the Utstein reporting method was designed to provide a uniform tool for reporting survival from cardiac arrest and to compare survival rates across different systems. Utstein reporting therefore compares those arrests, which are thought to be of cardiac aetiology, are by-stander witnessed and present in a shockable rhythm. However, this study is seeking to derive a universal TOR CDR, and the Utstein template itself is inappropriate for use



in these circumstances, as it would exclude certain subsets of cardiac arrest that are of interest to this study (e.g. those presenting with PEA or asystole and unwitnessed OHCA).

## **5.1 Study design**

Phase 1 was a retrospective cohort study that reviewed all consecutive cases of OHCA that were treated by clinicians within the Trust during a single 26-month period. From this pre-existing dataset adult patients were identified whose OHCA was of presumed cardiac aetiology and who were also transported to hospital. These data were collected by the Trust Governance Department from patient report forms (PRFs) that are completed by ambulance crews following every patient contact. The dataset included patient characteristics as well as any treatment provided and pertinent ambulance intervals. These variables included: patient age and sex; response interval (time of call to the first response stopping on- scene); ambulance interval (time of call to the first ambulance arriving on scene); treatment interval (interval between ambulance arrival and initiation of transport to hospital), travel interval (interval from scene to hospital); presence of witnesses to the arrest (whether bystander or ambulance crew); presence of bystander CPR; whether the initial cardiac rhythm was shockable (VF/pVT); whether defibrillation was administered at any time during the resuscitation; and presence of any return of spontaneous circulation (ROSC). The data also identified those patients who survived to discharge and those that died before discharge. These patient outcomes were collected from hospital records. The Trust transports OHCA patients to 33 main hospitals, from which two do not share survival data. Additionally, patients were transported or transferred to three hospitals outside of the Trust's geographical footprint. There is no agreement to share data with these hospitals.

The process of determining which variables to include in the final CDR involved several stages. First all variables were examined that were found in previous research to have an association with outcome<sup>111, 112, 149, 195, 196</sup>. These variables were then independently assessed for association with death. Arguably, by doing this there was the potential that the effect of small combined differences across the factors would be missed<sup>183</sup>. However, it was decided that at this stage that it was important to understand how each variable was associated with outcome and that the effects of small combined differences could be sacrificed in order to produce a simplified CDR, which would be clinically meaningful and applicable in the field.

Once associations with outcomes had been established, the implications of including the variables into a CDR were considered. At this stage the aim was to exclude any variables that would be unethical to include, as well as any variables that could not easily be established at the time of the incident.

Regression was then performed on the remaining variables, having first addressed the assumptions of the regression model. Finally, variables that were found to be positively associated with outcome were considered for the development of a TOR guideline. At this stage the aim was to simplify the potential CDR, whilst retaining its effectiveness. This required the developing of hypotheses, which could be adjusted at a later stage, if required.

Once a CDR was established by this method, it was retrospectively applied to the full dataset of transported, adult OHCA of presumed cardiac cause. This was done to establish whether the false positives (unexpected survivors) remained under the threshold of futility (defined previously as < 1%). It also enabled examination of the

unexpected survivors to decide whether any of the variables excluded during the earlier stages may have improved the results.

Finally, the newly derived CDR was compared with the results of applying the existing BLS and ALS CDRs to the same dataset. The aim here was to determine which rule resulted in fewer futile resuscitations being transported to hospital.

## **5.2 Study setting and population**

All OHCA resuscitation attempts that occurred between 1 April 2011 and 29 June 2013, and which were transported to hospital were reviewed. Patients were excluded from the study if no resuscitation was attempted (i.e. death was diagnosed due to presence of rigor mortis, decomposition, massive cranial and cerebral destruction, hemicorporectomy, incineration, hypostasis, or where a do not attempt CPR order was in place, in accordance with present Trust guidelines); they were under 18 years old; if the arrest was not presumed to have been of cardiac origin (i.e. the arrest was due to trauma, drowning, drug overdose, or some other medical cause); if the resuscitation attempt was terminated under current TOR guidelines (asystolic rhythm following twenty minutes of ALS); or if their outcome was unknown (Some hospitals did not provide follow up data).

## **5.3 Data analysis**

Statistical analysis was performed using IBM SPSS Statistics 22. For the purposes of analysing the data, death was considered as the positive outcome. Rather than predict survival, this approach attempts to determine when transport to ED is futile. It should also be noted that death was defined as any patient who was not discharged alive from hospital. No distinction was made between neurological outcomes of survivors, as this is beyond the scope of this thesis.

## 5.4 Patient disposition

Between 1 April 2011 and 29 June 2013, 8316 arrests were attended by ambulance crews in the Trust. Of these, 173 were under 18 years of age; 808 were not presumed to have been of cardiac origin (180 trauma, 26 submersion, 483 respiratory, 104 other and 14 unknown); 1268 resuscitations were terminated under the existing Trust policy; 704 were taken to hospitals who did not share survival data and 493 had no data available on survival.

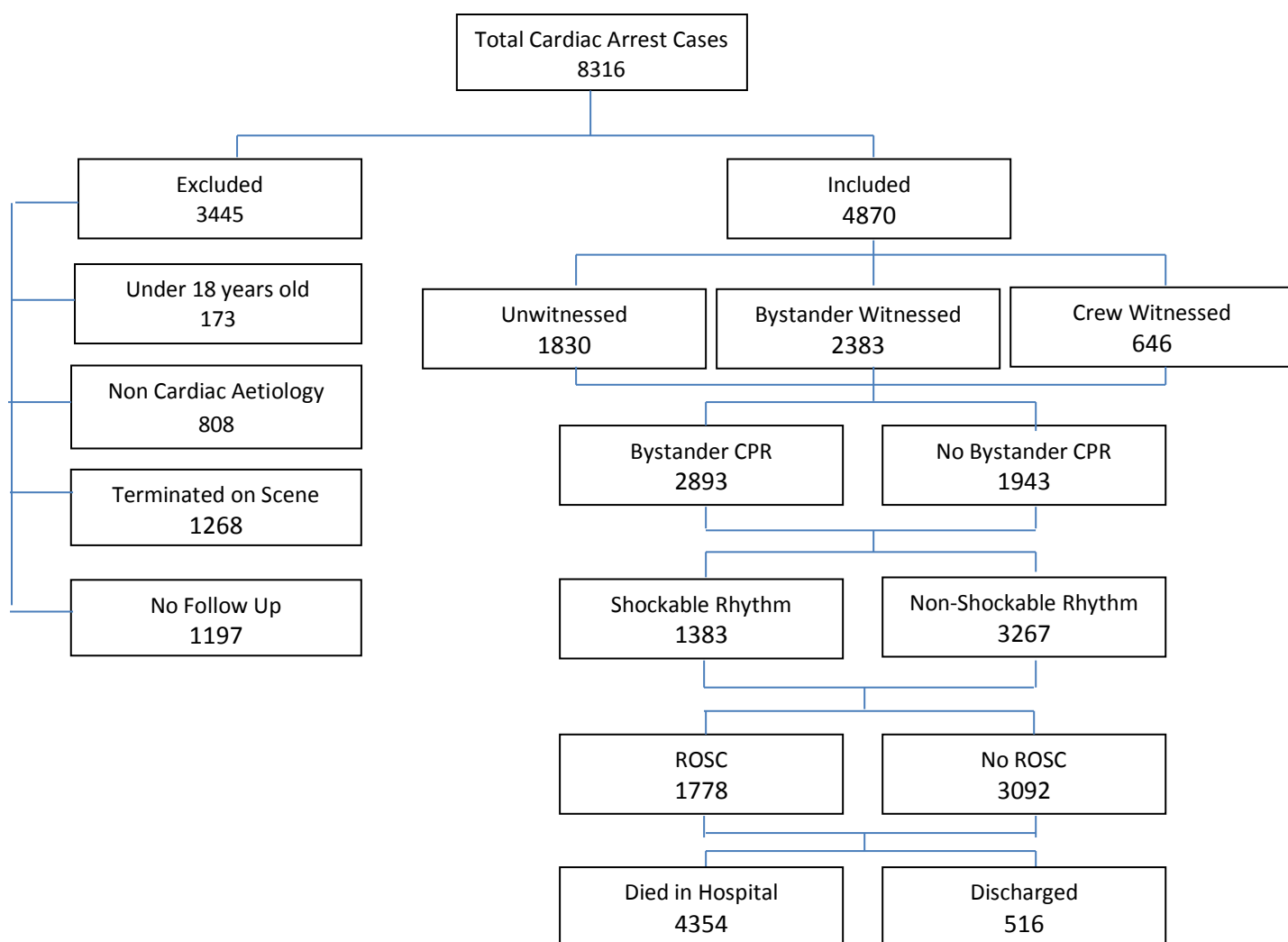
A total of 4,870 patients met the inclusion criteria for the study. Table 8 describes the out-of-hospital characteristics of all eligible patients according to follow-up status. The mean age for the patient group was 71.5 (sd 15.1) years, and 3033 (62.3%) were male. The mean response interval for the first response (Public access defibrillator, community first responder, rapid response vehicle etc.) was 6.67 minutes (sd 5.843). The mean response interval from ambulance activation to arriving on scene was 10.24 minutes (sd 7.72). The mean interval on scene was 28.72 minutes (sd 11.57) and the mean transport to hospital interval was 9.05 minutes (sd 6.78).

Of the 4870 patients with complete follow-up 4354 (89.4%) died and 516 (10.6%) survived to hospital discharge. In 4859 (99.8%) cases, it was recorded whether or not the arrest was witnessed. 2383 (48.9%) patients had an arrest witnessed by a bystander and 646 (13.3%) witnessed by an ambulance crew. In 100 (5.5%) of 1830 unwitnessed arrests the patients survived to discharge. Of the 2383 witnessed by a bystander, 276 (11.6%) survived. This compares to 140 (21.7%) of the 646 patients whose arrest was witnessed by ambulance crews. The presence of bystander CPR was recorded for 4836 (99.3%) of patients. Of the 2893 (59.8%) who received bystander CPR, 335 (11.6%) patients survived. In 1943 (40.2%) cases, bystander

CPR was recorded as not being present. 180 (9.3%) of these patients survived. In 34 (0.7%) cases, bystander CPR was not recorded. Of the 4870 patients, 4650 (95.5%) had a presenting cardiac rhythm recorded. Of these, 1383 (28.4%) presented with a shockable rhythm (1335 (27.4%) ventricular fibrillation and 48 (1%) ventricular tachycardia), 1667 (34.2%) presented with asystole and 1600 (32.9%) presented in PEA. 183 (3.8%) were recorded as other. For the purposes of analysis, this last group were listed as 'unknown'. 1833 (37.6%) patients were defibrillated during the resuscitation, so can be assumed to have had a shockable rhythm at some stage. 3035 (62.3%) were not defibrillated. ROSC was achieved at some point in the field for 1778 (36.5%). 3092 (63.5%) patients failed to achieve ROSC. Figure 1 illustrates the disposition of all OHCA patients utilised in this study.

<b>Characteristic</b>	<b>Present</b>
<b>Unwitnessed</b>	1830 (37.7%)
<b>Bystander witnessed</b>	2383 (48.9%)
<b>Crew witnessed</b>	646 (13.3%)
<b>Bystander CPR</b>	2893 (59.8%)
<b>No Bystander CPR</b>	1943 (40.2%)
<b>Shockable rhythm</b>	1383 (28.4%)
<b>Non-shockable rhythm</b>	3267 (67.1%)
<b>Defibrillated</b>	1833 (37.6%)
<b>Not defibrillated</b>	3035 (62.3%)
<b>ROSC</b>	1778 (36.5%)
<b>No ROSC</b>	3092 (63.5%)

**Table 8 - Characteristics of cardiac arrests**



**Figure 1 - Disposition of cardiac arrest patients**

### 5.5 Test for association

The first step in assessing which variables to include in the CDR was to consider the variables that have been shown to have an association with patient outcome, following findings of previous research<sup>111, 112, 149, 195, 196</sup>. These were patient age and sex; response interval; ambulance interval; treatment interval; travel interval; presence of witnesses to the arrest (bystander or ambulance clinician); presence of bystander CPR; Whether the initial cardiac rhythm was shockable (VF/pVT); whether defibrillation was administered at any time during the resuscitation; and presence of ROSC.

These variables were then independently assessed in order to establish odds ratios (ORs) and 95% confidence intervals (95% CIs) for the association of that independent variable with survival outcomes. Tests of association among the categorical variables were conducted using chi square test, and continuous data were analysed using the independent samples t test or Mann-Whitney U test, as appropriate. All comparisons were based on two-tailed tests. Categorical data included the patient's sex, whether the initial cardiac rhythm was shockable (VF/pVT), whether the arrest was witnessed by a bystander or by ambulance clinician, whether bystander CPR was performed, and whether the initial rhythm was shockable.

The chi-square test relies on two assumptions; firstly that each entity contributes to only one cell of the contingency table; and secondly that all cell frequencies should be greater than 5<sup>185</sup>. In each of the comparisons, these assumptions were met: No individual patient characteristic contributed to more than one cell and all cell frequencies were greater than 5. There was a statistically significant association between sex and outcome  $\chi^2(1) = 32.617$ ,  $p < 0.05$ ; between bystander CPR and outcome  $\chi^2(1) = 6.550$ ,  $p = 0.01$ ; between crew witnessed arrests and outcome  $\chi^2(1) = 95.885$ ,  $p < 0.05$ ; between initial shockable rhythm and outcome  $\chi^2(1) = 620.401$ ,  $p < 0.05$ ; between defibrillation and outcome  $\chi^2(1) = 389.034$ ,  $p < 0.05$ ; between bystander witnessed arrests and outcome  $\chi^2(1) = 4.565$ ,  $p = 0.33$ ; and between ROSC and outcome  $\chi^2(1) = 862.018$ ,  $p < 0.05$ .

The effects size for this categorical data was measured by using the odds ratio. The odds of survival for each significant variable were calculated, and then the odds of survival, if that variable was not present. The odds ratio was then calculated by dividing the first figure by the latter. Results are: ROSC (OR 48.9; 95% CI: 32.3 to

74.1); shockable rhythm (OR 13.8; 95% CI: 10.7 to 17.8); Defibrillated (OR 7.0; 95% CI: 5.6 to 8.7); Crew witnessed (OR 2.8; 95% CI: 2.3 to 3.5); Bystander witnessed (OR 1.2; 95% CI: 1.0 to 1.5); Male gender (OR 1.8; 95% CI: 1.5 to 2.2); Bystander CPR (OR 1.2; 95% CI: 1.1 to 1.6);

For the continuous variables, the independent-samples t-test was considered to determine whether the difference between these two independent outcome groups was statistically significant. However, the independent-samples t-test has six assumptions that first needed to be considered. The first three of these assumptions were met: (i) the presence of a continuous dependent variable; (ii) a dichotomous independent variable; and (iii) independent observations. The remaining three assumptions required testing: (iv) that there are no significant outliers within the two groups of independent variable in terms of the dependent variable; (v) that the dependent variable should be normally distributed for each of the independent variable groups; and (vi) That the variance is equal in each group of independent variables.

Outliers were found in all three groups of continuous data. The outliers appeared to be plausible and did not appear to be as a result of data entry errors and could not be assessed for accuracy of measurement, due to ethical restrictions of assessing data in any format other than that provided to the researcher. The outliers were therefore assumed to be genuine, and so there was no good reason to reject them as invalid. Rather than replace the values at this stage of data analysis, it was decided to run the non-parametric Mann-Whitney U test, as this is not affected by outliers to the same extent as the independent-samples t-test. The Mann-Whitney U test (also called the Wilcoxon-Mann-Whitney test) is a nonparametric rank-based test that determines if there are differences between two groups on a continuous



dependent variable. As with other tests, the Mann-Whitney U test, is subject to certain assumptions, which must be met before the test is run. These are: (i) There must be one dependent variable that is continuous or ordinal; (ii) There must be one independent dichotomous variable; (iii) There should be independence of observations; (iv) The distribution shape of scores for both scores of independent variables must be determined to have either the same or different shape. Where they are the same shape, the Mann-Whitney U test can be used to determine if there are differences in the medians of the two groups. If the two distributions are shown to have a different shape, the Mann-Whitney U test can be used to establish if there are differences in the distributions of the two groups.

Mann-Whitney U tests were run to determine if there were differences in age, response interval, ambulance interval, on-scene interval and travel interval between survivors and non-survivors. In each of the five tests distributions for both survival and non-survival groups were similar, as assessed by visual inspection. The median age was statistically significantly higher for non-survivors (75.16) than for survivors (63.79),  $U = 537,549$ ,  $z = -12.751$ ,  $p < .001$ . The median response interval was statistically lower for survivors (5 minutes) than for non-survivors (6 minutes),  $U = 965,192.5$ ,  $z = -5.246$ ,  $p < .001$ . The median ambulance response interval was statistically lower for survivors than for non-survivors,  $U = 1,052,974$ ,  $z = -2.327$ ,  $p = .02$ . The median on scene time was significantly lower for survivors (23 minutes) than for non-survivors (29 minutes),  $U = 771,253$ ,  $z = -11.645$ ,  $p < .001$ . The median transport interval was significantly higher for survivors (8 minutes) than for non-survivors (7 minutes),  $U = 1,217,107.5$ ,  $z = 4.091$ ,  $p < .001$ .

This stage of the analysis concluded that the independent variables age, sex, response interval, ambulance interval, on-scene interval, transport interval,

bystander witnessed, crew witnessed, shockable rhythm, defibrillation and ROSC may be associated with outcomes for adult pre-hospital cardiac arrest of assumed cardiac aetiology.

## **5.6 Variable selection for regression**

Having established which independent variables may be associated with outcomes for pre-hospital cardiac arrest; it was decided which of these to include in subsequent calculations to determine the CDR. At this stage the clinical application, as well as the operational and ethical implications of any variable was given priority. Both age and sex were shown to have an association with outcome. However, it is arguable that these two variables are potentially markers for unobserved comorbidities, so were considered inappropriate for use in the CDR. Additionally, age is a variable that may be difficult to establish on scene, particularly when there are no reliable bystanders to provide that information. Moreover, it was deemed ethically inappropriate to formulate a TOR CDR based on either of these patient characteristics. Intervals were also shown to have an association with outcome. Although these may well have a part to play in clinical decision-making on scene, their use in formulating the formal CDR was considered, but rejected at this stage.

There were also practical limitations to the use of response times in a CDR. Although response and ambulance intervals are currently used to assess whether a resuscitation attempt should be initiated <sup>68</sup>, it was thought that once the decision had been made to start a resuscitation, the response interval would be inappropriate to determine whether continued efforts were futile. Also, whilst the on scene interval was associated with survival, the interval spent on scene has a lot to do with the logistics and procedures surrounding the process of resuscitation and could not be seen as a causative indicator, without having an understanding of those other

factors. Travel interval cannot be assessed accurately whilst on scene and so was excluded from further consideration. It was accepted that these variables may have an interaction with the other variables, so to include them in any subsequent analysis may have unduly influenced the model, so were not included. Excluding these factors was consistent with the approach of Gold, Fahrenbruch, Rea, *et al*, discussed previously, which concluded that models should incorporate only physiological changes following cardiac arrests as a more accurate way to ascertain survival <sup>121</sup>.

### **5.7 Binominal logistic regression**

The next stage of evaluation was to perform regression on the remaining variables. As the dependent variable (survival) was dichotomous (i.e. a nominal variable with only two categories) and there was more than one independent variable, binomial logistic regression was required as the predictive model. Logistic regression is similar to multiple regression, but is used where the outcome variable is a categorical dichotomy, and where the predictor variables are categorical or continuous <sup>185</sup>. Unlike linear regression, logistic regression does not attempt to determine the predicted value of the dependent variable, but rather the probability of a case being in a particular group of the dependent variable having regard to the independent variables. This tool therefore enabled determination of whether the variables were predictors of a patient's outcome.

Like other statistical techniques, binary logistic regression carries certain assumptions, which need to be met in order to generalise the results of the test to the universal population. The first five assumptions relate to the study design and are:

1. There is a dichotomous dependent variable.

2. There are two or more independent variables, which can be either continuous or nominal.
3. There should be independence of observations.
4. The categories of the dichotomous dependent variable and all the nominal independent variables should be mutually exclusive and exhaustive.
5. There should be, in general, a minimum of 15 cases per independent variable

These assumptions were met with this dataset. The dependent variable was dichotomous (Death or survival); all independent variables were dichotomous; the observations were independent as patients could be categorised as 'yes' or 'no' for each of the independent and the dependent variable: They could not be both.

The last three assumptions relate to the nature of the data. These are:

1. That there is no multicollinearity. i.e. that no independent variables in the model are approximately predicted by a linear combination of any other independent variables in the model.
2. There is a linear relationship between the continuous independent variables and the logit transformation of the dependent variable.
3. That there are no significant outliers.

Having established the first five assumptions, the predictor variables were assessed for multicollinearity. Multicollinearity refers to an approximate linear relationship between two or more independent variables. A tolerance of less than 0.2 or a Variance Inflation Factor (VIF) of greater than 5 were taken to indicate a multicollinearity problem <sup>197</sup>. Using these indicators, none of the predictor variables showed multicollinearity. There were no continuous independent variables, so the assumption of a linear relationship was not an issue.

Binominal logistic regression was then performed to determine whether survival could be predicted, based on bystander witnessed, bystander CPR, crew witnessed, initial shockable rhythm, defibrillation and ROSC. The binominal logistic model is used to quantify the effect of a predictor as an odds ratio or log odds ratio.

The baseline analysis showed that without any independent variables, the 'best guess' will assume that no participants would survive. This assumption would correctly classify 90.6% of cases (Table 9). This figure is high, but not unexpected, as the number of survivors over all is low.

Observed	Predicted		Percentage correct
	Died	Survived	
Died	4170	0	100%
Survived	435	0	0
Overall Percentage			90.6%

**Table 9 – Baseline analysis**

	B	S.E.	Sig.	Exp(B)	95% C.I. for EXP(B)	95% C.I. for EXP(B)
					Lower	Lower
Bystander CPR	-.079	.137	.566	.924	.707	1.209
Bystander witnessed	.300	.157	.057	1.349	.992	1.836
Crew witnessed	1.232	.198	.000	3.430	2.327	5.054
Shockable	2.368	.244	.000	10.676	6.619	17.220
Defibrillated	.208	.250	.405	1.231	.754	2.010
ROSC	3.692	.226	.000	40.110	25.749	62.483
Constant	-6.537	.273	.000	.001		

**Table 10 - Logistic regression predicting survival**

The coefficients for the associations between OHCA characteristics and survival are shown in Table 10. The regression model explained 51.1% (Nagelkerke  $R^2$ ) of the variance in survival and correctly classified 91.8% of all cases. From the perspective of death as a positive outcome <sup>166</sup>, sensitivity was 99.3%, specificity was 20.0%,

positive predictive value was 92.30% (95% CI; 91.49% to 93.06%) and negative predictive value was 73.73 % (95% CI; 64.83% to 81.40%). The low specificity at this stage was not unexpected. With only 10.6% survival to discharge, it was unlikely that this model would be able to identify these patients, without including any non-survivors. However, the process did identify the predictor variables likely to be of use for creating the CDR. Of the six predictor variables three were statistically significant. These were shockable rhythm, ROSC and crew witnessed.

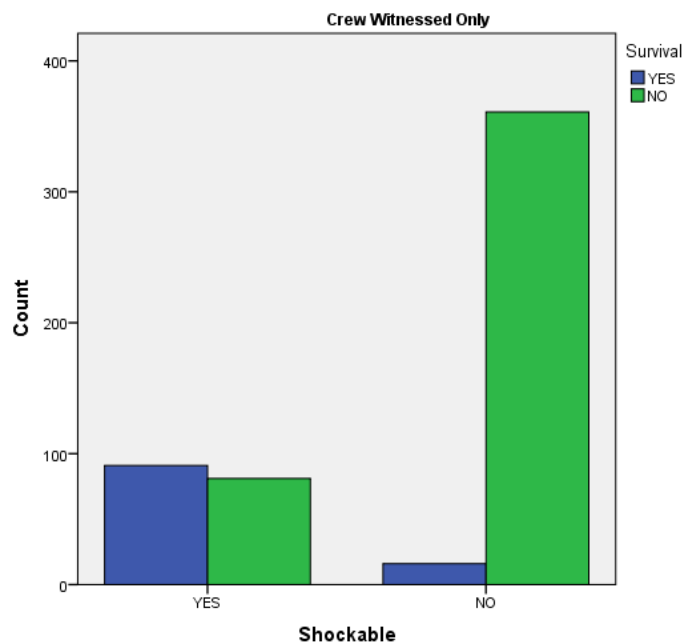
### **5.8 Selecting TOR CDR criteria**

Having established the variables with a strong association to outcomes, each variable was further assessed for inclusion in the final TOR CDR. Bystander witnessed, bystander CPR defibrillation at any time were not significantly associated with outcome, so were excluded from the CDR. Three variables were shown to have a strong negative association with death; ROSC (OR = 40.1; 95% CI: 25.7% to 62.5%), initial shockable rhythm (OR = 10.7; 95% CI: 6.6% to 17.2%), and crew-witnessed (OR = 3.4; 95% CI: 2.3% to 5.0%). Independently, ROSC had a specificity of 95.4% (95% CI: 93.2% to 97%); a sensitivity of 70.5% (95% CI: 69.1% to 71.8%); PPV of 99.2% (95% CI: 98.9% to 99.5%) and NPV of 27.7% (95% CI: 26.7 to 28.7). A presenting shockable rhythm had a specificity of 81.7% (95% CI: 77.7% to 85.2%); a sensitivity of 75.6% (95% CI: 74.3% to 76.9%); PPV of 97.6% (95% CI: 97% to 98%); and NPV of 25.7% (95% CI: 24.4% to 27.1%). The variable 'crew witnessed arrest' had a specificity of 27.1% (95% CI: 23.3% to 31.2%); a sensitivity of 88.4% (95%CI: 87.4% to 89.3%); PPV of 91.1% (95% CI: 90.6% to 91.5%); and NPV 21.7% (95% CI: 19% to 24.6%).

This analysis suggests that the variables with the strongest association with outcome were ROSC and initial shockable rhythm. By itself, a lack of ROSC predicted death in all but 24 (0.8%) cases. Consideration was given to utilising the absence of ROSC as the sole predictor of death. However, whilst 0.8% is within the predetermined definition of futility, there was a potential that this may increase beyond 1% when applied to a different dataset. Therefore it was decided not to use ROSC as a predictor in isolation at this stage, but would nevertheless be reviewed at later phases of the study. Crew witnessed arrests showed similar sensitivity, but much lower specificity than the other two variables. This is due in part to the low numbers of patients who suffer a crew witnessed arrest, so the majority of survivors are not witnessed by crews. Nevertheless, a large proportion of patients who had a crew witnessed arrest went on to survive (21.7%). However, it was postulated that the variable of crew witnessed arrest may be interacting with the variable relating to the cardiac rhythm the patient presents with. As discussed earlier, VF arrests are the most common initial rhythm <sup>39</sup>, and VF respond well to early defibrillation <sup>57</sup>. Therefore, a patient who arrests in the presence of a responder with a defibrillator at hand may be likely to have definitive treatment very quickly after that arrest occurs. If this hypothesis is correct, then it is the fact that a patient has presented in a shockable rhythm in the presence of a responder that is important, rather than the proximity of the responder per se.

To examine this further those patients who had a crew-witnessed cardiac arrest were selected. A chi-square test for association was conducted between initial shockable rhythm and survival. All expected cell frequencies were greater than five. There was a statistically significant association between initial shockable rhythm and survival,  $\chi^2(1) = 178.251$ ,  $p < .0001$ . Of the 549 patients suffering a crew-witnessed cardiac

arrest, for whom all appropriate data was available, 172 (31.3%) had an initial shockable rhythm. Of these, 91 (52.9%) survived. Of the remaining 377 (68.7%) who suffered a non-shockable arrest, 16 (4.3%) survived (Figure 2)



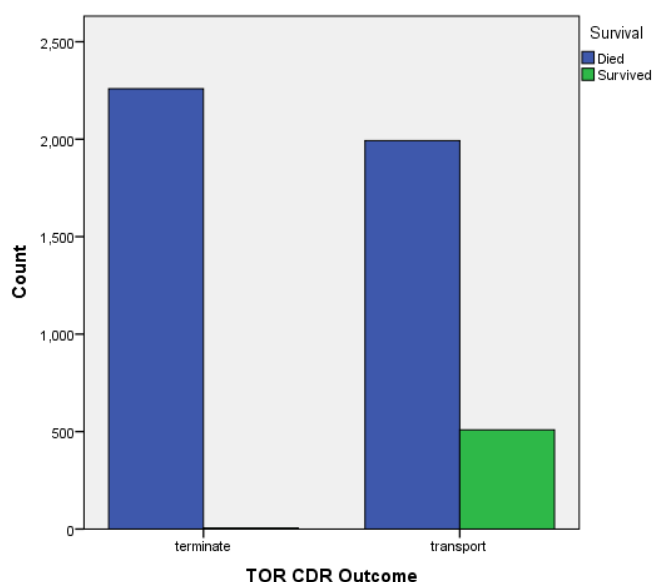
**Figure 2 – Outcomes vs rhythm (crew witnessed only)**

These results suggest that the presence of a shockable rhythm interacts with the association between crew-witnessed arrests and survival. It was therefore decided not to include the variable ‘crew-witnessed arrest’ in the CDR at this point. This would be reconsidered later.

Consequently only initial shockable rhythm and ROSC were considered for inclusion in the proposed TOR CDR. As a result, the TOR CDR proposes TOR for adult OHCA of suspected cardiac aetiology, in addition to existing guidelines on asystolic patients, where the presenting rhythm is not a shockable rhythm, and where no ROSC is achieved before transport. Patients not within this group would be transported to hospital. Retrospective application of this CDR to the original sample



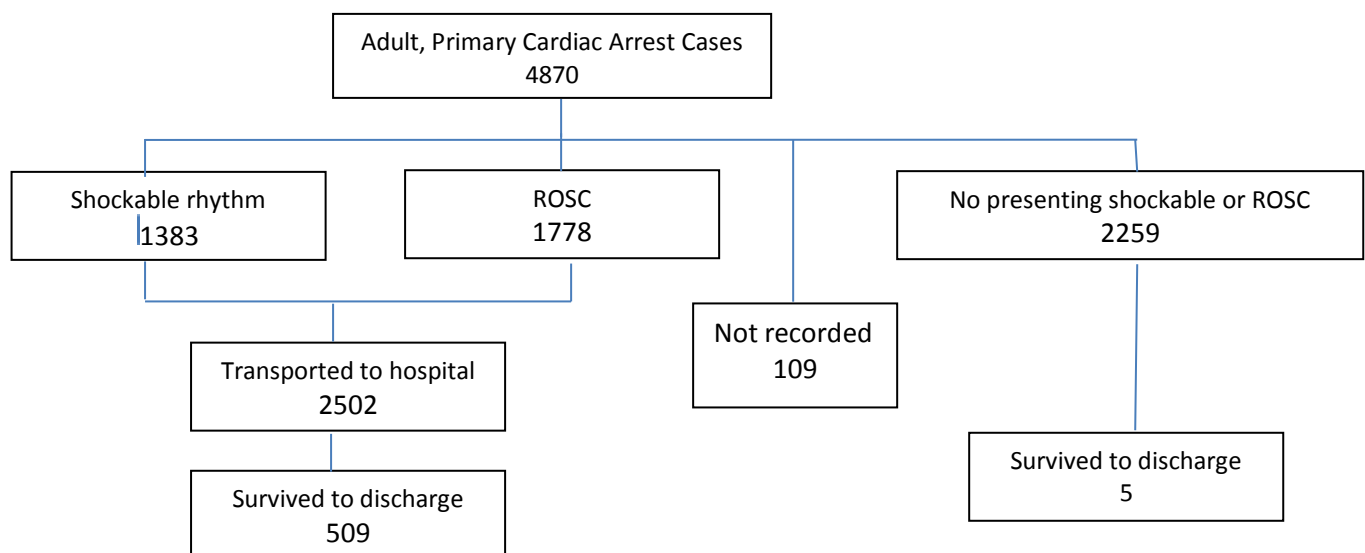
(Figure 3) showed that all but 5 patients suffering OHCA who survived to discharge were within the group identified as requiring onward transport (positive predictive value = 99.8%; 95% CI: 99.5% to 99.9%, specificity = 99.0%; 95% CI: 97.7% to 99.7%). The sensitivity and negative predictive values of this TOR CDR are also of note (53.1%, 95% CI: 51.6% to 54.6%, and 20.3%, 95% CI: 19.8% to 20.9%). The study aimed to determine which resuscitation attempts would not benefit from transport to ED. Although it is not possible to determine who will survive an OHCA, the sensitivity of the test indicates how effective it is at ensuring that only those patients likely to survive are transported to hospital. A lower sensitivity suggests that greater numbers of futile attempts are recommended for transport.



**Figure 3 – Application of TOR CDR**

Application of the TOR CDR would have resulted in five unexpected survivors, which equates to 0.2% of those categorised as futile (Figure 4 and Table 11). This is below the threshold of 1% for futile interventions<sup>198</sup>. The CDR also recommended termination of resuscitation for 2264 (47.6%) of 4761 patients (taking into account missing data), or a transport rate of 52.4%. This compares favourably with those

validations reported in previous chapters, where the mean transport rate was 59.5% (lowest 25.1%, highest 94.5%). It should be remembered however that the transport rates reported in the previous studies include all patients with OHCA of presumed cardiac aetiology. The transport rates reported here refer only to those patients currently transported, so do not include those who end up in an asystolic rhythm. As previously noted, some 1268 OHCA's were already terminated under existing TOR guidelines. As these patients were excluded from the present study, they are not included in the total figures for transport rate. This results in a higher overall transport rate than would be the case if all OHCA's of cardiac aetiology are calculated. However, the purpose of this study was to identify futile transport from those patients currently transported to hospital. Despite this, the TOR CDR compares favourably with the other CDRs in terms of transport rate.



**Figure 4 - Derivation of TOR - Disposition of cardiac arrest patients**

<b>TOR Guideline</b>	<b>Died</b>	<b>Survived</b>	<b>Total</b>
<b>Terminate</b>	2259	5	2264
<b>Transport</b>	1993	509	2502
<b>Total</b>	4252	514	4766

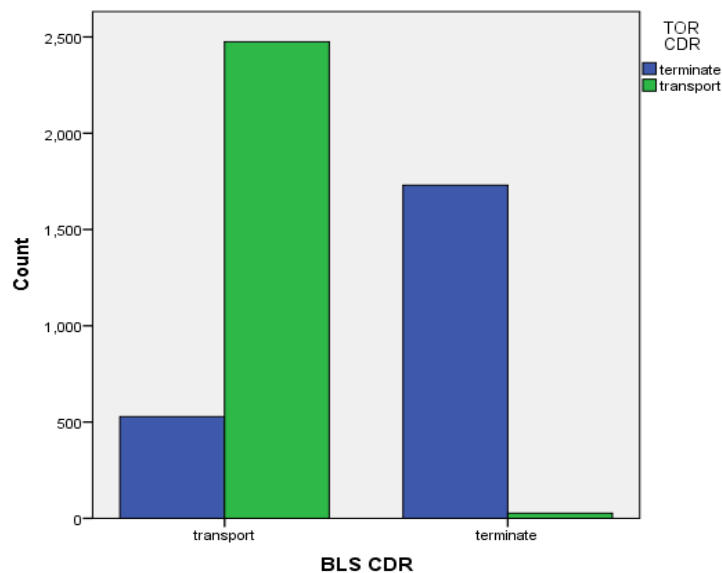
**Table 11 - Table of results**

### **5.9 Comparison with other CDRs**

In order to determine the efficacy of the CDR in relation to the BLS and ALS CDRs, they were also applied to the data. The BLS CDR criteria derived by Verbeek, Vermeulen, Fahim *et al* included crew-witnessed arrest, defibrillation at any time or ROSC at any time <sup>199, 200</sup>. Although this CDR appears at first to be very similar to the TOR CDR derived here, there are some important differences. The inclusion of crew-witnessed arrests has already been discussed. The other difference is the use of defibrillation as a variable. Whereas the TOR CDR created here uses an initial shockable rhythm as a component, the BLS TOR uses defibrillation at any time. This would capture all patients within the group presenting with shockable rhythm, but would also include patients who were initially presenting in an asystolic, or PEA rhythm, and subsequently developed fibrillation. This is potentially a much wider group of patients.

Applying the BLS CDR to the dataset resulted in 3067 patients being recommended for transport, of whom 513 (16.7%) survived. 1797 patients were recommended for termination, and 3 (0.2%) survived. This equates to a specificity of 99.4% (95% CI: 98.1% to 99.8%), a positive predictive value of 99.8% (95% CI: 99.5% to 100%), sensitivity of 41.2% (95% CI: 39.8% to 42.7%) and a negative predictive value of 16.7% (95% CI: 15.4% to 18.1%). This would have resulted in a transport rate of

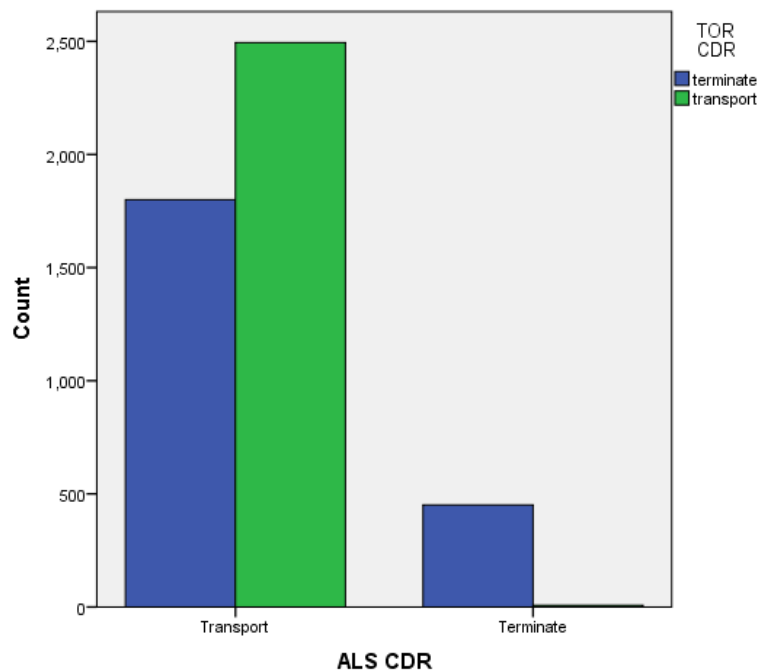
63.1%. Figure 5 illustrates the increased number of transported patients resulting from the BLS CDR.



**Figure 5 - Comparison of BLS CDR with the derived CDR.**

The ALS guideline derived by Morrison, Verbeek, Vermeulen *et al* recommends termination for patients where the arrest was not witnessed by either bystanders, or ambulance clinicians, there was no bystander CPR, no defibrillation at any point and no ROSC <sup>112</sup>. The inclusion of bystander witnessed and bystander CPR into the CDR greatly increases the number of potentially futile attempts that are transported to hospital. Applying these criteria to the dataset resulted in 478 patients recommended for termination; with 2 (0.4%) of these surviving. 4379 patients were recommended for transport. Of these 513 (11.7%) survived. This equates to a specificity of 99.6% (95% CI: 98.4% to 99.9%); a positive predictive value of 99.6% (95% CI: 98.3 to 99.9%); sensitivity of 11.0% (95% CI: 10.0% to 11.9%); and a

negative predictive value of 11.7% (95% CI: 10.8% to 12.7%). The transport rate, when applying this CDR is 90.2% (Figure 6 and Table 12).

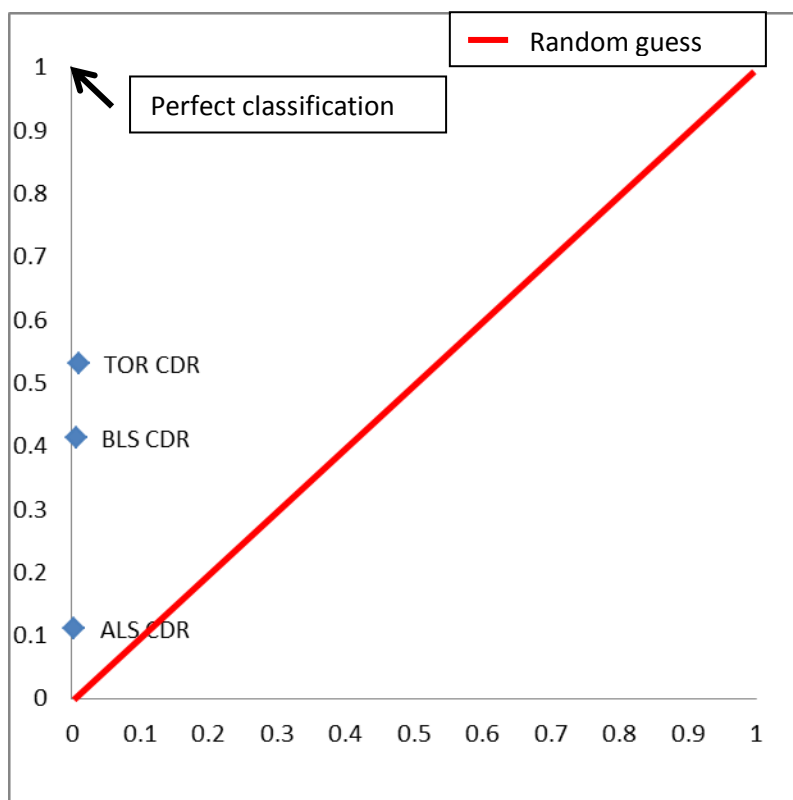


**Figure 6 - Comparison of ALS CDR with the derived CDR.**

Against this retrospective cohort of patients, both the BLS and ALS CDRs result in fewer unexpected survivors (3 and 2 survivors respectively). However, this is at the cost of increased transport rates (63.1% and 90.2% respectively), which reduced the sensitivity of the tests from 53.1% to 41.2% and 11.0% respectively. When plotted on a ROC space (sensitivity vs (1 – specificity) plot) (Figure 7), the TOR CDR clearly shows the best predictive power, when compared to either the BLS CDR or the ALS CDR (The closer a result is to the upper left corner, the better it predicts, and the distance from the random guess line indicates how much predictive power a method has).

	TOR CDR	BLS CDR	ALS CDR
Specificity	99.0% (95%CI: 97.7% to 99.7%)	99.4% (95% CI: 98.1% to 99.8%)	99.6% (95% CI: 98.4% to 99.9%)
Sensitivity	53.1% (95% CI: 51.6% to 54.6%)	41.2% (95% CI: 39.8% to 42.7%)	11.0% (95% CI: 10.0% to 11.9%)
PPV	99.8% (95% CI: 99.5% to 99.9%)	99.8% (95% CI: 99.5% to 100%)	99.6% (95% CI: 98.3 to 99.9%)
NPV	20.3% (95% CI: 19.8% to 20.9%)	16.7% (95% CI: 15.4% to 18.1%)	11.7% (95% CI: 10.8% to 12.7%)
Transport rate	52.4%	63.1%	90.2%

**Table 12 – Characteristics of CDRs**



**Figure 7 – ROC space comparing three CDRs**

### 5.10 Unexpected survivors

Retrospective application of the TOR CDR resulted in 5 unexpected survivors. Of these, one was recorded as an 85 year old female, who had an unwitnessed cardiac arrest in a public place. The patient is reported to have been in an asystolic cardiac arrest, albeit with bystander CPR, for eight minutes until the ambulance arrived.

Following 26 minutes of treatment on scene and a further ten minutes transport interval to hospital and without being defibrillated at any point, or regaining ROSC, she is reported to have been intubated, but cannulation was failed and no medications administered. She is reported to have survived to discharge. The second was a 64 year old male. He is reported to have had an unwitnessed cardiac arrest in a place of residence. He was asystolic and received no bystander CPR, though the response interval was only three minutes. This patient was intubated, cannulated and received 1mg of adrenaline. He was defibrillated twice and although not reported as regaining ROSC for the duration of 22 minutes of treatment on scene and 54 minutes transport interval. The third was a 70 year old male. He is reported to have had an unwitnessed cardiac arrest in a place of residence. He received no bystander CPR and was in a PEA rhythm on arrival of the first response, which arrived three minutes from the time of the call. He was intubated and cannulated, but did not achieve ROSC before transport. He is reported to have survived to discharge. The fourth was a 20 year old female. She is reported to have had an unwitnessed cardiac arrest in a place of residence. There was bystander CPR and she was in asystole on arrival of the first response after three minutes. She was intubated and cannulated and received adrenaline as part of ALS protocol. She was also reported to have been defibrillated three times. She is reported not to have achieved ROSC before transport. She was treated on scene for 27 minutes and the transport interval was 16 minutes. The last unexpected survivor was an 89 year old male. He is reported to have had an unwitnessed cardiac arrest in a place of residence. There was no bystander CPR and his presenting rhythm was PEA on arrival of the first response after one minute. He was cannulated and administered adrenaline, but the intubation attempt is reported to have failed. He was treated on

scene for 31 minutes and the transport interval was eight minutes. He did not achieve ROSC at any point during this interval, but reportedly survived to discharge.

Of these unexpected survivors, 3 (60%) were male. The mean age was 67.57 (sd 27.25). The mean response interval was 3.2 minutes (sd 2.95), ambulance interval 9.4 minutes (sd 2.97), on scene interval 30.4 minutes (sd 9.29), and transport interval 17 minutes (sd 20.92). None were witnessed arrests (either by bystander or crew). Two (40%) received bystander CPR. Two (40%) were in an initial PEA rhythm and three (60%) were in asystolic rhythms. Two (40%) received defibrillation at some point during the resuscitation. None of the survivors were witnessed arrests. Whilst the BLS CDR excludes from termination those patients with crew-witnessed arrests and the ALS CDR also excludes those with bystander-witnessed arrests, the decision was made not to include witnessed arrest as part of the CDR, for the reasons discussed earlier. The exclusion of this variable from the CDR did not result in unexpected survivors. Although two unexpected survivors received bystander CPR, to include this as a variable requiring transport would have resulted in marginal improvement to specificity (99.4%; 95% CI: 98.3% to 99.9%), it would have reduced sensitivity (22.5%; 95% CI: 21.3% to 23.8%). Moreover would have increased the transport rate from 52.4% to 79.9%. Similarly, both the BLS and ALS CDRs included defibrillation at any point during the arrest as a variable requiring transport. To include this would have captured two of the unexpected survivors. However, this would also have resulted in a marginal improvement to specificity (99.4%; 95% CI: 98.3% to 99.9%), it would have reduced sensitivity (46.3%; 95% CI: 44.8% to 47.8%) and resulted in another 305 patients being transported to hospital, increasing the transport rate to 58.6%.



The data gained from these unexpected survivors did not therefore suggest that the derived CDR should be adjusted before further validation. However, the details of each of these events did raise an element of doubt about the veracity of the original dataset. On the face of it, it does appear improbable that some, if not all of these unexpected survivors actually survived to discharge, if the data surrounding the conditions of their cardiac arrests are correct. For example, the second unexpected survivor appears to have survived an unwitnessed OHCA despite being found in an asystolic rhythm, receiving no bystander CPR, and not achieving ROSC for the full 66 minutes of the event. Although this is a possibility, it does appear unlikely on the face of it. However, due to the ethical restrictions on accessing anything other than the original dataset, it could not be ascertained whether there had been a clerical error in determining survival, whether the surrounding circumstances were annotated incorrectly, or whether this was, in fact, an unexpected survival. In the interests of transparency, this and the other cases were retained in the dataset.

### **5.11 Strengths and limitations**

This phase of the study was able to consider 4870 consecutive OHCA incidents, which is a large number of incidents, all of which were collected independently. Nevertheless, there are several limitations to this study, which must be mentioned. Firstly, our study utilised a register of OHCA, maintained by the Trust, and collected by auditors from data presented by crews on PRFs. This team are highly trained as auditors and there are systems in place to corroborate evidence if required, which include the information from ambulance control centres and reviews of local press reports. However, the auditors are non-clinicians and so there is the potential that interpretation may be lost in the audit process. Also, whilst using this register ensures a high degree of external validity, it does mean that the study was

observational by nature. Because the database was examined through a secondary analysis of the TOR CDR rather than prospectively, data integrity and validity are potential limitations. This has been highlighted in the previous section. Furthermore, this database was a 'convenience sample', in that the data was not collected for the purposes of determining futility of resuscitation attempts. The dangers of using such 'convenience samples' were highlighted by Harrell and include the following: study subjects may not be representative of the population; important predictors may not have been collected; key variables may not be present for large numbers of subjects<sup>183</sup>. That the dataset collected all resuscitation attempts performed by Trust clinicians over the given period negates the first point, but the second element is of note. However, the comprehensive nature of the data gathered, due its inclusion in national reporting, make that unlikely. The final point does need to be emphasised, nevertheless. As a case-control study, this study suffered from a limitation common to all such studies: missing data could not be retrieved retrospectively. Several of the receiving hospitals in the Trust's locality did not share data on survival, and a further 72 (1.5%) of cases did not record either initial cardiac rhythm or ROSC, so were excluded from the study. The ROSC variable used in this study includes the occurrence of ROSC at arrival in the emergency department as well as in the pre-hospital setting, and it was not possible to distinguish momentary ROSC events and those which persisted for longer intervals. This may inflate the accuracy of the CDR, which should include only ROSC which persists long enough for a decision to be made to transport the patient.

During the analysis of data, no account was taken of the qualifications of the crew(s) involved with each cardiac arrest. As technician crews cannot terminate resuscitations under the present TOR guidelines, there is the potential that

resuscitations deemed futile under the present guidelines were transported to hospital, as the efforts were not permitted to be terminated on scene. This may have exaggerated the effect of the CDR being derived, as these patients would not have been included, had the efforts been terminated by Paramedics on scene under existing guidelines. It is of note, however, that none of the five CDR-positive survivors were attended by technician crews. The retrospective nature of the study failed to determine whether Paramedics in the field would be able to apply the rule correctly. However, as Paramedics within the Trust have been successfully applying a different TOR decision rule for over ten years, and regularly follow clinical decision rules relating to other conditions, this is not considered to be prohibitive. Also, the study was limited to a single ambulance Trust. Although, as a large Trust, covering both densely urban and sparsely rural areas, the population is not heterogeneous; any results may not be transferable to other localities and emergency systems.

It should also be mentioned at this stage that whilst the derived TOR CDR appears be worthy of further study, advances in resuscitation science and post-resuscitation care could quickly invalidate any specific decision rule <sup>114</sup>. As noted previously, there is some potential that measuring ETCO<sub>2</sub> may prove a useful predictor for futility. However, the data collected for this study did not include ETCO<sub>2</sub>, so could not be assessed as a variable.

Having derived the TOR CDR it was important that the rule was also validated. The following chapter discusses the validation of the rule against a separate retrospectively collected dataset.

## **6. Chapter six - Retrospective validation (Phase 2)**

In the previous chapter a TOR CDR was derived, which appeared to show that it was possible to determine the futility of transporting an adult suffering an OHCA of cardiac aetiology to hospital if the patient did not present initially with a VF/pVT arrest and did not achieve ROSC on scene. This chapter aims to provide initial validation of the rule by applying it to a second cohort of patients, from a retrospectively collected dataset. Both the BLS and ALS CDRs will also be applied to the cohort to compare the results. Application of the rule to a retrospective cohort will provide assurance at level 4 in the validation hierarchy, meaning that it is validated, but not to the extent that it is clinically applicable at this stage <sup>141</sup>. It was decided that rather than moving directly to a prospective validation, which would be time-consuming and require a lot of organisational coordination, it was important to ensure that the CDR was first tested against a second data set of OHCA patients, and in particular to compare it with the other CDRs in terms of identifying futile transportation. Any adjustments to the CDR that this may highlight could then be made before the prospective validation process was undertaken in a subsequent phase.

### **6.1 Study design**

Phase 2 was a retrospective cohort study. It was conducted in order to validate the TOR CDR established in phase 1 against an independent data set of patients and to compare the results with the application of existing CDRs. The TOR CDR sought to find those variables that could be used to identify futile resuscitation attempts amongst adult patients currently transported to hospital with continuing resuscitation. As for phase 1, this phase included all patients aged 18 years of age or older who were treated for an OHCA of suspected cardiac aetiology and who were

subsequently transported to hospital. Patients were enrolled between 1 April, 2014, and 31 March 2015.

## **6.2 Study setting and population**

As for phase 1, this phase of the study was a multi-centre design, using data from the Trust that covers a population of over seven million people, and which attends over one million emergencies per year. The study population was made up of consecutively enrolled adult patients who were treated for OHCA by the Trust's clinicians (Paramedics and technicians) between 1 April 2014 and 31 March 2015. These data were collected as in phase 1 by the Trust Governance Department's trained auditors from PRFs completed by clinicians during or immediately after each patient contact, as well as survival outcomes from hospital records. Patients were excluded from the phase 2 if they were under 18 years old; if no resuscitation was attempted (i.e. death was diagnosed before resuscitation was attempted); if the arrest was not presumed to have been of cardiac origin (i.e. their arrest was due to trauma, drowning, drug overdose, or other non-cardiac cause); if the resuscitation attempt was terminated under current TOR rules (i.e. asystole after 20 minutes of Advanced Life Support (ALS)); or if their outcome was unknown (Some hospitals did not provide follow up data).

Data for each resuscitation event included all elements gathered at phase 1: patient age and gender; response interval; ambulance interval; treatment interval; transport interval; presence of witnesses to the arrest (bystander or ambulance crew); presenting cardiac rhythm; presence of bystander CPR; whether defibrillation was attempted at any point during the resuscitation attempt; and presence of ROSC.

### **6.3 Outcome measures**

The primary outcome measure was survival to hospital discharge. The aim was to determine whether the TOR CDR could accurately predict those patients who would not survive to discharge, and how it compared to existing CDRs in the identification of futile transportation. The TOR CDR, established in phase 1 recommends termination of resuscitation where the initial presenting rhythm is not shockable (i.e. is PEA/asystole), and where there is no ROSC before transport to hospital.

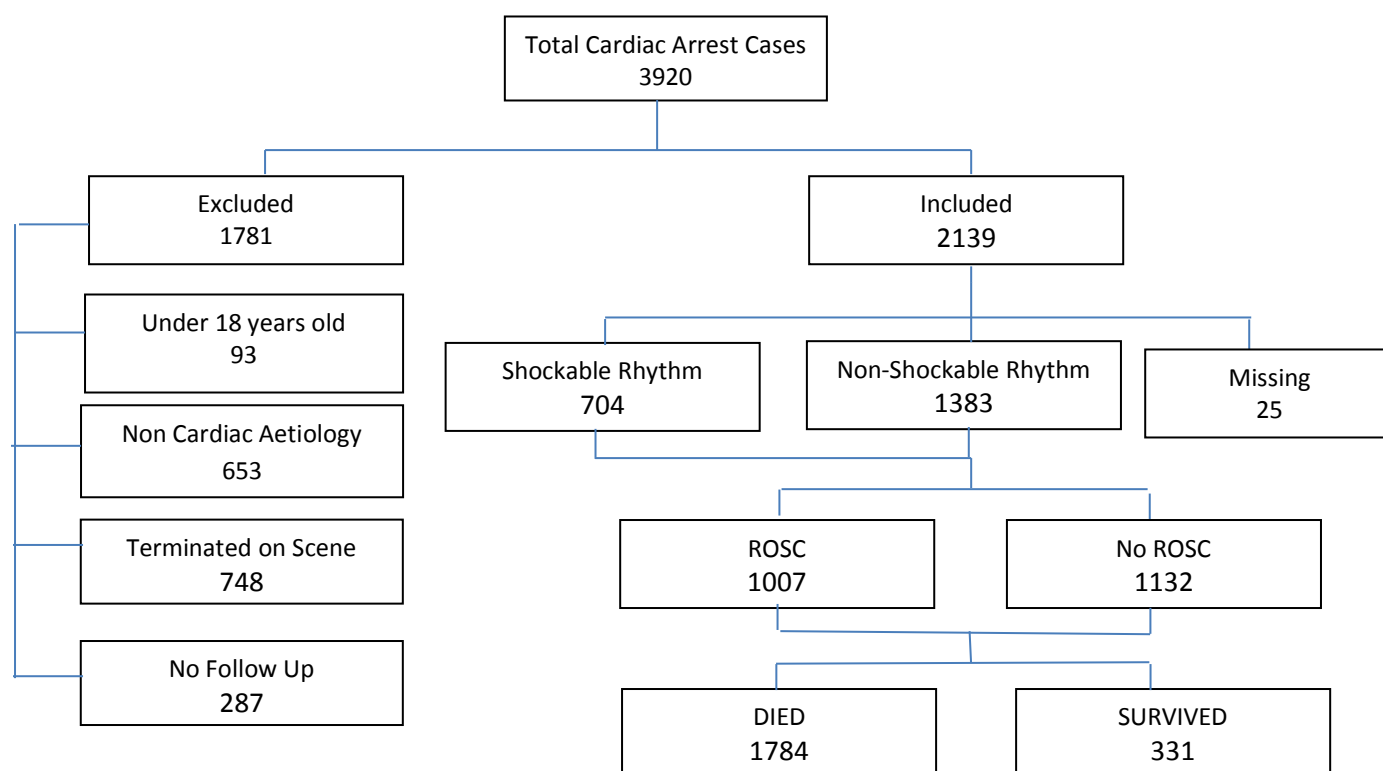
The test characteristics for each of the three CDRs included in this phase were sensitivity, specificity, and positive and negative predictive values. Ideally a CDR would recommend termination for all those patients who will not survive to hospital discharge, as the aim of the CDR is to reduce futile transportation. As such the sensitivity of the rule (the probability that the CDR will recommend termination when transport is futile) is an important characteristic. This will indicate how effective the rule is at reducing the number of futile transportations. To support it, the transportation rates were also determined. These were based on the number of patients that the CDR recommended for transport to ED. Survival amongst the group was also calculated. It is also important that any CDR should not recommend TOR if there was a potential for the patient to survive. The specificity of the rule (the probability that the CDR will recommend transport when the patient survived) and the positive predictive value (the probability that the patient would die if the rule recommends TOR) were the key test characteristics to assess this.

### **6.4 Statistical analysis**

The Statistical analysis was performed using SPSS for Windows (SPSS ver. 22, Chicago, IL). For the purposes of analysing the data, death was considered as the positive outcome.

## 6.5 Results

Between 1 April 2014 and 31 March 2015, a total of 3920 OHCA's were attended by ambulance crews in the Trust. The disposition of these patients is shown in figure 8.



**Figure 8 – Retrospective validation - Disposition of cardiac arrest patients**

Of the 3920 patients, 93 (2.4%) were excluded as they were under 18 years of age. Of the remainder, 653 (17.1%) cardiac arrests were not of cardiac origin (123 trauma; 8 submersion; 373 respiratory; 40 asphyxiation; 40 hanging; 67 drug overdose; and 2 unknown). Another 748 (19.5%) were terminated under the existing Trust TOR guidelines; and 287 (7.5%) had no data available on survival outcomes. Therefore a total of 2139 patients met the inclusion criteria for the study. The mean age for the patient group was 69.6 (sd 15.7) years, with the youngest being 18 years and the oldest 102 years. 1373 (64.2%) were male. The mean response interval for

the first response (Community first responder, rapid response vehicle, or ambulance) was 8 minutes 8 seconds (sd 7:02). The mean on-scene interval was 38 minutes 27 seconds (sd 14:32) and the mean transport interval from the scene to hospital was 10 minutes 34 seconds (sd 11:04).

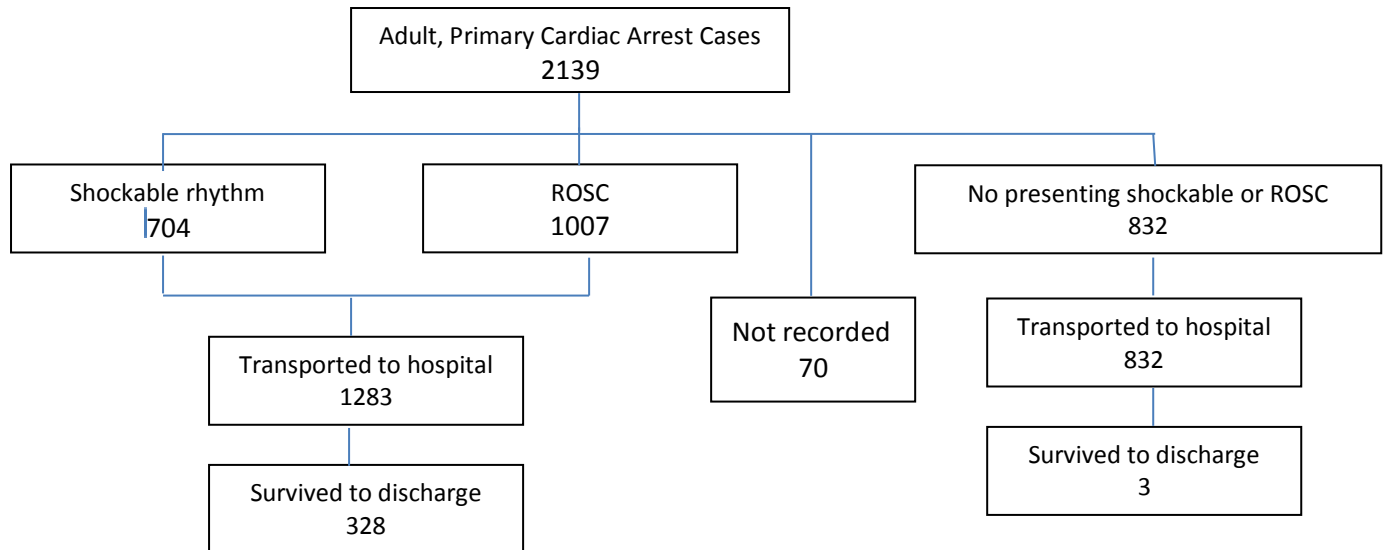
Characteristic	Present	% of total
<b>Shockable rhythm</b>	704	32.9%
<b>Non-shockable rhythm</b>	1383	67.3%
<b>ROSC</b>	1007	47.1%
<b>No ROSC</b>	1132	52.9%
<b>Survival to discharge</b>	331	15.4%

**Table 13 – Selected characteristics of cardiac arrests included in the phase 2**

Table 13 shows the relevant characteristics of all patients included in this phase of the study. Of 2139 patients, who met the inclusion criteria for the study, 704 (32.9%) presented with an initial shockable rhythm; 665 (31.1%) presented with asystole; 700 (32.7%) presented in PEA; 2 (1.4%) were reported as bradycardic; 16 (0.7%) were recorded as ‘other’; and 25 (1.2%) had missing data. 1007 (47.1%) achieved ROSC at some point and 1132 (52.9%) did not. 331 (15.4%) patients survived to hospital discharge (233 (10.9%) with unknown neurological deficit, 5 (0.2%) with known neurologic deficit, and 93 (4.3%) with no neurologic deficit). 1808 (84.5%) died in hospital (1560 (72.9%) died within 24 hours, and 248 (11.6%) died after 24 hours).

The TOR CDR derived in phase 1 recommended termination for 832 (38.9%) and transportation for 1283 (60.0%) of the patients currently transported in Phase 2. 24 (1.1%) could not be classified due to missing data. Of the 832 patients that the TOR CDR recommended termination, 3 (0.4%) survived to hospital discharge. The remaining 328 survivors were recommended for transport (Figure 9).





**Figure 9 - Retrospective validation – Results**

Observed	TOR CDR	
	Transport	Terminate
<b>Died</b>	<b>955</b>	<b>829</b>
<b>% within CDR</b>	<b>74.4%</b>	<b>99.6%</b>
<b>% within total</b>	<b>45.2%</b>	<b>39.2%</b>
<b>Survived</b>	<b>328</b>	<b>3</b>
<b>% within CDR</b>	<b>25.6%</b>	<b>0.4%</b>
<b>% within total</b>	<b>15.5%</b>	<b>0.1%</b>
<b>Total</b>	<b>1283</b>	<b>832</b>

**Table 14 - Retrospective validation – Table of results**

Table 14 shows the results of applying the TOR CDR in phase 2. The TOR CDR recommended termination for 829 (46.5%) of the 1784 patients who died (sensitivity = 46.5%; 95% CI: 44.1% to 48.8%). Of the 832 patients for whom the TOR CDR recommended termination, 829 (99.6%) died and three (0.4%) survived. This represents a positive predictive value of 99.6% (95%CI; 99.0% to 99.9%) and specificity of 99.1% (95% CI: 97.4% to 99.8%). Transportation was recommended

for 1283 (60.7%) patients. Of these 328 survived. This results in a negative predictive value of 25.6% (95%CI; 23.2% to 28.1 %). The transportation rate using the TOR CDR was 60.7%.

## **6.6 Comparison with other CDRs**

As with the derivation of the CDR in phase 1, the existing BLS and ALS CDRs were applied to the data to compare results. Applying the BLS TOR to the dataset resulted in 1557 patients being recommended for transport, of whom 331 (21.3%) survived. 582 (27.1%) patients were recommended for termination, and all of these survived. This equates to a specificity of 100% (95% CI: 98.9% to 100%), a positive predictive value of 100% (95% CI: 99.3% to 100%), sensitivity of 24.4% (95% CI: 22.6% to 26.1%) and a negative predictive value of 15.5% (95% CI: 14.0% to 17.1%). This would have resulted in a transport rate of 72.8%.

Applying the ALS TOR criteria to the dataset resulted in 102 (4.8%) patients recommended for termination; with none of these surviving. 2026 (95.2%) patients were recommended for transport. Of these 331 (16.3%) survived. This equates to a specificity of 100% (95% CI: 98.6% to 100%); a positive predictive value of 100% (95% CI: 95.5% to 100%); sensitivity of 4.7% (95% CI: 3.9% to 5.8%); and a negative predictive value of 14.0% (95% CI: 12.7% to 15.5%). The transport rate, when applying this CDR is 95.2%.

	TOR CDR	BLS CDR	ALS CDR
Specificity	99.1% (95% CI: 97.4% to 99.8%)	100% (95% CI: 98.9% to 100%)	100% (95% CI: 98.6% to 100%)
Sensitivity	46.5% (95% CI: 44.1% to 48.8%)	24.4% (95% CI: 22.6% to 26.1%)	4.7% (95% CI: 3.9% to 5.8%)
PPV	99.6% (95%CI; 99.0% to 99.9%)	100% (95% CI: 99.3% to 100%)	100% (95% CI: 95.5% to 100%)
NPV	25.6% (95%CI; 23.2% to 28.1 %)	15.5% (95% CI: 14.0% to 17.1%)	14.0% (95% CI: 12.7% to 15.5%)
Transport rate	60.7%	72.8%	95.2%

**Table 15 – Characteristics of CDRs in phase 2**

## 6.7 Discussion

There were fewer patients in this phase of the study, when compared to the previous phase (2139 vs 4870). However the mean ages were broadly comparable (69.6 (sd 15.7) vs 71.5 (sd 15.1)), as was the percentage of male patients (64.2% vs 62.3%). A Mann-Whitney U test was run to determine if there were differences in median response intervals, on scene intervals and transport intervals between the validation and derivation studies. Distributions of all intervals between the datasets were similar, as assessed by visual inspection. All intervals were found to be statistically significantly higher in the validation dataset than in the derivation dataset ( $p < .001$ ). Despite these increased intervals, proportionately more patients survived in this phase of the study (15.5%), than the previous (10.6%) Again this is statistically significant ( $p < .001$ ). However, proportionately more presented with an initial shockable rhythm (32.9% vs 28.4%;  $p < .001$ ), which may account for some of the increased survival. Also, whereas 36.3% achieved ROSC in the derivation phase, this increased to 47.1% during this phase ( $p < .001$ ). That the Trust saw an increase in ROSC during the validation period is not unexpected. Mandatory training for all staff during that period included a session on effective compressions and a procedure was introduced whereby at least four responders, including where

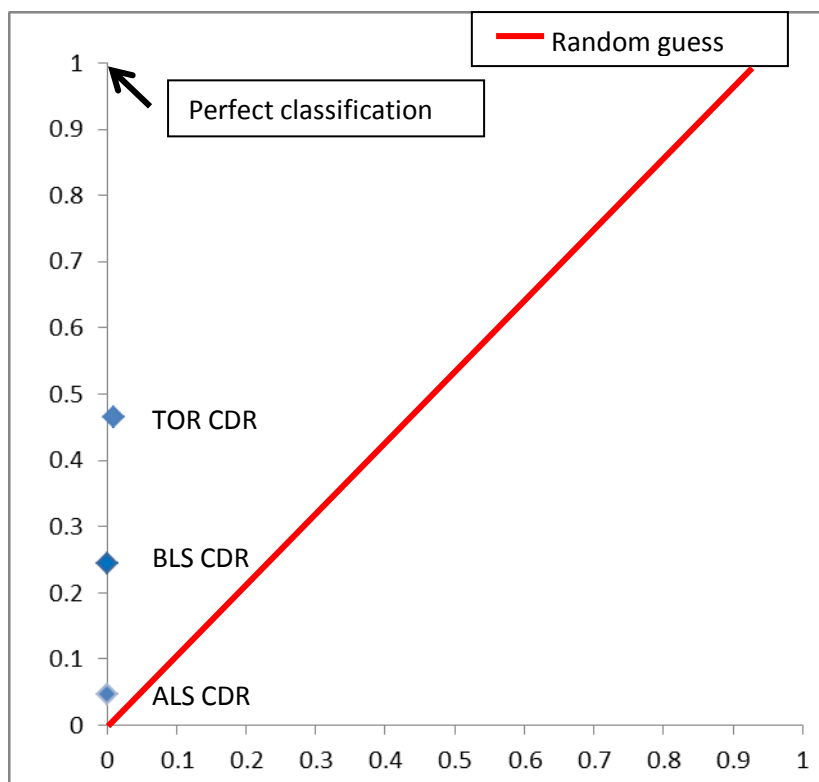
possible a senior clinical lead, were sent to all OHCA incidents. Both these procedures were aimed at improving OHCA outcomes, though whether they had a direct influence on the increase in ROSC cannot be confirmed. Nevertheless, with increased numbers of ROSC, and increased incidence of initial VF/pVT, it is not surprising that the transport rate increased during this stage of the study from 52.5% to 60.7%. Despite this increase in transport rate, the percentage of unexpected survivors increased from 0.2% to 0.4%, resulting in a reduced PPV of 99.6% from 99.8% and specificity of 99.1% from 99.8%.

Following discussions from phase 1, it was considered whether the presence of ROSC would in and of itself be a good indicator of survival, and if so, whether the lack of ROSC could be used as an indicator of futility. However, in this sample the 12 patients survived despite no presence of ROSC. This equates to 1.1% of the total number without ROSC ( $n = 1132$ ), which is outside the acceptable limits for futility, as discussed earlier. This confirmed the inclusion of presenting shockable rhythm as an essential element of the TOR CDR at this stage.

The TOR CDR compared favourably with the pre-existing CDRs. Applying the BLS and ALS CDRs to this patient cohort demonstrated both increased transport rates (+12.1% for the BLS CDR and +34.5% for the ALS CDR). As part of our second objective was to reduce the number of futile transportations to hospital, the sensitivity of each CDR is of particular importance. The TOR CDR was able to identify more futile resuscitations than either of the other CDRs (829 vs 582 and 102 respectively), which would result in fewer unnecessary transports. Neither the BLS or ALS CDRs had any unexpected survivors, but this was at the expense of identifying far fewer futile transports (331 (21.3%) and 102 (4.8%) vs 829 (46.5%)). It was not an expectation that the TOR CDR would result in all potential survivors being identified,

which is why the limits of futility were agreed as 1% and not zero. The aim was to reduce, as far as practicable, the number of futile transports, whilst remaining within the 1% definition of futility for unexpected survivors. In this retrospective cohort, the CDR achieves this, and does so with a lower transportation rate than either the BLS or ALS CDRs.

When plotted on a ROC space (sensitivity vs (1 – specificity) plot) (Figure 10), the TOR CDR clearly shows the best predictive power, when compared to either the BLS CDR or the ALS CDR



**Figure 10 – ROC space comparing three CDRs**

## **6.8 Unexpected survivors**

Application of the TOR CDR resulted in three unexpected survivors. The first was a 43 year old male, who had a bystander witnessed cardiac arrest in a public place. He received no bystander CPR and the first response on scene arrived one minute from

the collapse. The treatment interval was 17 minutes and the travel interval was 16 minutes. The first monitored rhythm was asystole, though he did receive one shock from a defibrillator, suggesting that at some point he was in a VF/pVT rhythm. The patient was treated with a supraglottic airway and although cannulation was successful, it is recorded that he received no adrenaline. This is inconsistent with guidelines for a patient in cardiac arrest, but the data collected does not explain why this should be the case.

The second patient was a 64 year old male. The call to scene interval for this patient was nine minutes, the on scene interval was 57 minutes and the travel interval was seven minutes. This patient suffered an unwitnessed cardiac arrest at home. Bystander CPR was performed. The patient is reported to be asystolic on arrival of the ambulance crew. He received endotracheal intubation, intravenous access and adrenaline. He was defibrillated three times, the first being reported as 26 minutes after the ambulance arrived on scene, but was reported not to gain ROSC on scene.

The final unexpected survivor was a 63 year old female, who suffered a crew-witnessed cardiac arrest in the ambulance. The presenting rhythm was PEA. The patient was intubated and cannulated. She received adrenaline, but was not defibrillated at any point. The data for this patient records the cause of arrest as presumed cardiac. However there are notes attached to 'presenting complaint' that say "fitting/cardiac arrest". No other details of this patient are available.

In the light of these unexpected survivors it was considered whether other variables should be added into the TOR CDR. In particular was considered the inclusion of crew-witnessed arrests, as this is included in the BLS CDR and had a significant association with outcome in the original model. However, whilst inclusion of this

variable would have reduced the number of unexpected survivors in this cohort to two, it would also increase the number futile transports from 955 (53.5%) to 1105 (77.1%), taking into account missing data. The resulting CDR would equate to a specificity of 99.4% (95% CI: 97.8% to 99.9%); a positive predictive value of 99.7% (95% CI: 98.9% to 99.9%); sensitivity of 38.6% (95% CI: 36.4% to 40.9%); and a negative predictive value of 22.9% (95% CI: 22.3% to 23.6%). After consideration it was decided that the impact on transport rates did not justify the inclusion of this variable into the CDR.

The inclusion of bystander witnessed arrests and defibrillation were also considered for inclusion in the CDR. Neither of these variables were significant in the original model, but were considered here for the purposes of transparency. Like the crew-witnessed variable, the bystander-witnessed variable would have reduced the unexpected survivors to two in this cohort of patients. However, this would have been at the cost of 1674 transports (391 more than the TOR CDR). This equates to a specificity of 99.4% (95% CI: 97.8% to 99.9%); a positive predictive value of 99.6% (95% CI: 98.4% to 100%); sensitivity of 24.6% (95% CI: 22.6% to 26.7%); and a negative predictive value of 19.7% (95% CI: 17.8% to 21.6%). The transport rate, when adding this variable to the CDR is 79.1%. The inclusion of defibrillation at any time would have reduced the number of unexpected survivors in this cohort to one. As before, this is at the expense of increased transportation and equates to a specificity of 99.7% (95% CI: 98.3% to 100%); a positive predictive value of 99.9% (95% CI: 98.3% to 100%); sensitivity of 38.5% (95% CI: 36.3% to 40.8%); and a negative predictive value of 23.1% (95% CI: 20.9% to 25.4%). The transport rate, when applying this to the CDR is 67.5%. Although this variable appeared to be the most favourable to add to the CDR at this stage, in phase 1 of this study defibrillation

did not show a strong association with outcome (OR = 1.231; 95% CI: 0.754% to 2.010%). Therefore it was decided not to add it to the CDR at this stage.

## **6.9 Strengths and limitations**

It is important to validate any predictive model before it is implemented <sup>145</sup>. By evaluating the performance of the CDR against this separate cohort of patients, it was shown that the CDR was not data-dependant at phase 1, and that it works satisfactorily for patients other than those from whose data it was derived. Nevertheless, this phase of the study, like the previous, used a pre-existing dataset compiled by Trust auditors. As such, it suffers from many of the limitations described for phase 1 of this thesis. It retains a high degree of external validity, as the data was collected independently of the investigators, but data integrity and validity are potential limitations. This was highlighted when the data concerning the three unexpected survivors were reviewed. There were some inconsistencies with the reported information, such as the lack of administration of adrenaline for the first patient, despite apparent ongoing resuscitation efforts. This in itself suggests that ROSC was achieved; negating the need for adrenaline, but this is not evident in the information available to this study. Similarly, there were potential inconsistencies in the recording of the cause of the cardiac arrest for the third patient, as discussed earlier.

As with phase 1, the data was provided as a single dataset and missing data could not be retrieved retrospectively. As a result there was relevant data was missing for 70 patients, who could not therefore be designated as either termination or transport under the rules of the TOR CDR, so were excluded from the final results.

The most fundamental limitation of this phase was that it was retrospective in nature, so failed to determine whether Paramedics in the field would be able to apply the



rule correctly. As noted previously, this was accepted before phase 2 was started, but was seen as a necessary step before a prospective cohort study was undertaken in phase 3.

Having now completed the retrospective validation and confirmed that the TOR CDR retained its validity on an independent data set of patients, the next chapter reports on the subsequent prospective validation of the rule.

## 7. Chapter Seven - Prospective validation (Phase 3)

### 7.1 Study design

Previous chapters have discussed the derivation and subsequent retrospective validation of a TOR CDR. Phase 3 took the form of a prospective cohort study and was conducted to validate the same CDR. This was seen as an essential step to take in the validation process. As Altman and Royston have noted, the reason for validating a prognostic model is to establish that the model works acceptably for patients other than those from whose data the model was derived <sup>145</sup>. This was achieved in phase 2. However, they go on to make the distinction between statistically validated and clinically validated models. This is akin to the categories defined by McGinn Guyatt, Wyer *et al* and discussed earlier that require at least one prospective validation study and a change in clinical behaviour in order for a CDR to be considered a level 1 validation. As Burstein noted, “Any classification system... should be proved to be a workable tool before it is used in a discriminatory or predictive manner” <sup>201</sup>. During this phase of the study the TOR CDR could not be used as a tool to decide patient outcomes, but rather it was intended to show that ambulance clinicians were able to apply it prospectively, and that it was able to predict patient outcome satisfactorily.

Before the start of the study, all Paramedics and EMTs within the Trust were informed of the prediction rule via emails and Trust bulletins. During the course of the study reminders were published in the Trust’s clinical newsletter (CLEAR Vision) and via the Trust’s in-house social network site. Also emails were sent to all the Trust’s Advanced and Senior Paramedics (clinical leads) informing them of the study and requesting them to highlight the study to clinicians, encourage completion of the data collection forms and to collect completed forms and forward them to the

investigator. Twenty volunteers were also recruited throughout the Trust. They were tasked with ensuring that clinicians continued to complete the data collection forms throughout the study period. In order to ensure availability, electronic data collection forms were emailed to staff and paper copies were also left on ambulance stations.

## **7.2 Study setting and population**

Before the study was initiated, the location of the study was considered. Three options were reviewed. The first was to limit the study to a small selection of clinicians within the Trust. The Trust has a cadre of Senior and Advanced Paramedics, numbering approximately 250 clinicians. Limiting the study to this cohort would ensure increased compliance with completing the CDR. However, whilst the Trust endeavours to send a clinical lead to each OHCA, this cannot be guaranteed. This would result in a limited number of OHCA attended and could result in low study numbers. The second option was to limit the study to a single area of the Trust. Again, this would ensure maximum data capture within the selected area, as the investigator would have had a smaller area on which to concentrate their efforts for data capture. However, with the relatively low number of OHCA within the Trust, it was determined that to limit the area would require the study to run for a longer interval, which was prohibited by the timescales of this thesis. This method could also introduce limitations to the generalisability of the study, in that it would contain results from only a small population, with a limited number of receiving hospitals. The final option was to include all clinicians within the Trust, and aim to capture a greater number of OHCA, over a shorter interval. This method would create results that could be generalised across the Trust. However, it increased the risk that data would be lost, due to the investigator having to gather data from a much wider area, and including greater numbers of clinicians. Nevertheless, it was

decided to continue with this method in order to gather the most data in the time frame available. The risk of lost data was mitigated by the use of regular information being passed to clinicians and the use of champions throughout the Trust to ensure maximum data capture.

Next, it was necessary to determine the minimum number of OHCA required to provide statistical power to prove the CDR. A balance needed to be established between obtaining enough data and the efforts required to collect the data from across a large geographical area, whilst maintaining clinicians' reliability in completing the data collection forms. To establish a minimum number, a sample size calculator that assesses a dichotomous endpoint for two independent sample study was utilised<sup>202</sup>. To do this the CDR was equated to a treatment, with survival as the primary endpoint. The previous phases showed a survival rate of 10.6% and 15.5%. The mean of these (13.1%) was taken as the incidence of expected survival within the transport group. Survivors within the termination groups were 0.2% and 0.4% for the previous phases. Again the mean of these (0.3%) was taken to represent the expected incidence of survivors within the termination group. An alpha of 0.05 was used. This represents the probability of a type-I error, or finding a difference when a difference does not exist. Using 0.05 indicates a 5% chance that a significant difference is actually due to chance and is not a true difference. A beta value represents the probability of a type-II error, which occurs when it is believed there is no effect, when in reality there is. It has been suggested that the maximum acceptable probability of a type-II error should be 0.2 (or 20%)<sup>185</sup>. This means that in a population of 100 in which an effect does exist, that effect would be missed in 20 cases (i.e. 1 in 5 genuine effects would be missed). In order to reduce that possibility, a beta value of 0.1% was used here. Beta is directly related to study

power ( $\text{Power} = 1 - \text{Beta}$ ). Using a beta cut-off of 10% (0.1) indicates a 10% chance that a significant difference is missed. Applying these figures meant that a minimum sample size of 78 was required in each group. The previous phases of this study suggested a mean of 182 suitable OHCA per month. With approximately 13.1% survival, this equates to approximately 23 survivors per month. Therefore it was concluded that 3.4 months of data were required to ensure 78 survivors. However, as there was a risk of lost data, it was decided that a five month period of data collection would be used.

The study population was made up of adult patients (persons 18 years of age or older) who were treated for an out-of-hospital cardiac arrest, which was of presumed cardiac cause between August 2015, and December 2015 in the geographical area of the Trust. The Trust had a policy in place at the time of the study that aimed to ensure at least four rescue personnel were mobilised to each resuscitation event. At least one of these should be an ALS provider. Ideally, at least one should also be a clinical lead. All patients who were under 18 years of age and any who were thought to be pregnant were excluded, as well as those patients who had an arrest presumed to be of non-cardiac origin (e.g., trauma or asphyxia). Pre-hospital care was documented with the use of a standard PRF used by ambulance personnel throughout the Trust.

All statistical analysis was performed with SPSS for Windows (SPSS ver. 22, Chicago, IL). The TOR CDR was evaluated as a diagnostic test, and test characteristics were calculated. The test characteristics included sensitivity, specificity, as well as positive and negative predictive values. An ideal test would recommend termination for all patients who did not subsequently survive to hospital discharge. The sensitivity of the rule would indicate how well the CDR recognised

these futile attempts. Additionally, the PPV of the test will show how likely it is at a patient will not survive, when the CDR recommends termination. In addition to this, the CDR should not recommend termination if the patient could potentially survive OHCA. This is indicated by the specificity of the rule. The NPV will determine how likely it is that a patient will survive when the decision rule recommends transport. Finally, the transport rate was determined, as this has particular relevance for ambulance operations, as it gives an indication of the impact on ambulance resources of implementing the CDR.

### **7.3 Study protocol**

Data collection forms were made available to all NWS clinicians, both in paper and electronic format. Each form included all relevant elements of the CDR in the form of a flow chart and tables, and a final section that indicated either 'termination' or 'transport' (Appendix 6). Both the preceding literature and the form itself highlighted that the information was for study purposes only and should not affect any decisions relating to the patient's ongoing care or transport, which would be decided on existing Trust guidance and policy. Following any OHCA, where the patient was transported to hospital, the ambulance clinicians were asked to complete one of these forms. Patients were subsequently categorised by the attending clinician according to the recommendations of the CDR (termination or transport). For patients who did not achieve ROSC before they were transported to the hospital, and whose initial presenting rhythm was non-shockable (PEA / Asystole), the rule recommended the termination of resuscitation. For patients who did have ROSC before transport was initiated, or who presented initially with a shockable rhythm (VF/pVT), the prediction rule recommended transport. Data were identified by date and incident number only. No patient identifiable information was collected or recorded at

any point in the study, in accordance with the requirements of ethical approval for the project. Because of the clinical setting and that the patients in this study were suffering an OHCA, the standard requirement of written informed consent by patients was waived. However, all clinicians were made aware that they were under no obligation to complete the forms for this study.

The clinical leads and volunteers at each ambulance station reviewed the data collection forms for accuracy. Once checked, the forms were sent via Trust internal mail, or scanned and emailed using the Trust's secure email system, to the investigator. The data were then collected using a spread sheet program (Excel 2010, Microsoft Corp., Redmond, WA) and statistical analyses performed with SPSS for Windows (SPSS ver. 22, Chicago, IL). Problems relating to missing data were resolved by requesting additional information from the clinical leads at each site, or contacting the attending clinicians personally either by telephone or email. Other data required for the study was collected by reviewing the anonymised copy of the PRFs that were completed for each incident. These copies of the PRF are used for audit purposes by the Trust and contain all relevant clinical data, but have all patient details obscured.

#### **7.4 Outcome**

The investigator was able to obtain information on the patients' outcomes from hospitals, via the Trust's audit team. The data received included the date, incident number and patient outcome, including neurologic status if this was known. The data was received six to eight weeks after the cardiac arrest event. Not all receiving hospitals were willing to share data with the Trust, so the outcomes of some patients remained unknown. Outcomes were categorised as: survived to hospital discharge (neurological deficit unknown); survived to hospital discharge (with neurological

deficit); survived to hospital discharge (no neurological deficit); Died in Hospital (<24 hrs); Died in Hospital (>24hrs). For the purposes of this study the outcomes were analysed as a binary measure of “survived” (the first three outcomes) or “died” (the last two outcomes).

## **7.5 Results**

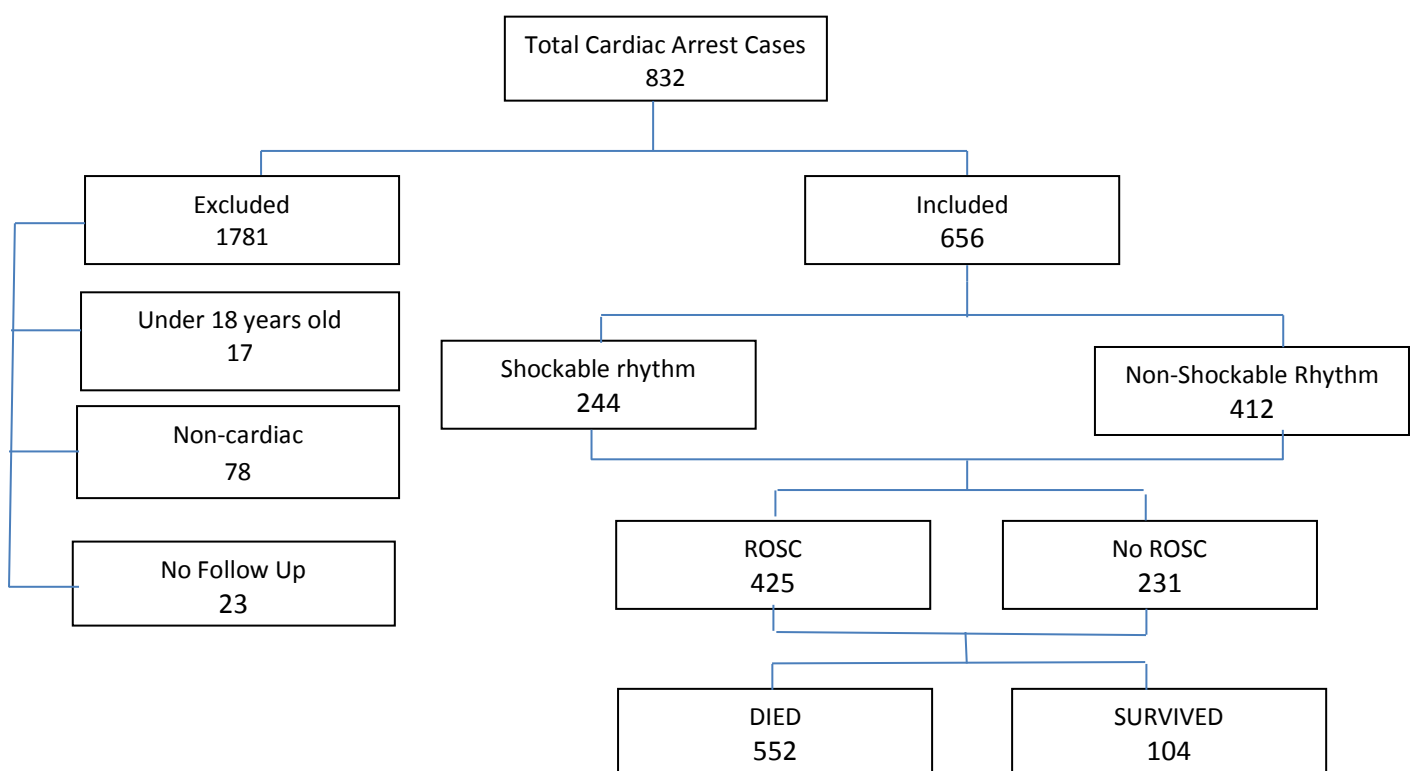
Between 1<sup>st</sup> August 2015 and 31st December 2015, a total of 832 CDR forms were received from ambulance clinicians. Of these, 17 (2%) related to patients who were less than 18 years old, so were excluded from the study. A further 78 (9.6%) recorded OHCA as non-cardiac aetiology, so were also excluded. Of the remaining 737, there were no outcome results provided by the receiving hospitals for 23 (3.1%). Of the 656 included patients the mean age was 70.3 years (sd 14.9) and 431 (65.7%) were male. The mean response time for these incidents was 8 minutes (sd 16), the mean on scene interval was 40 minutes (sd 16), and the mean travel interval was 11 minutes (sd 8).

Of 656 patients, who met the inclusion criteria for the study, 244 (37.2%) presented with an initial shockable rhythm, 425 (64.8%) achieved ROSC. 104 (15.9%) patients survived to hospital discharge (75 (11.4%) with unknown neurological deficit, 3 (0.5%) with known neurologic deficit, and 26 (4%) with no neurologic deficit). 552 (84.1%) died in hospital (454 (69.2%) died within 24 hours, and 98 (14.9%) died after 24 hours).

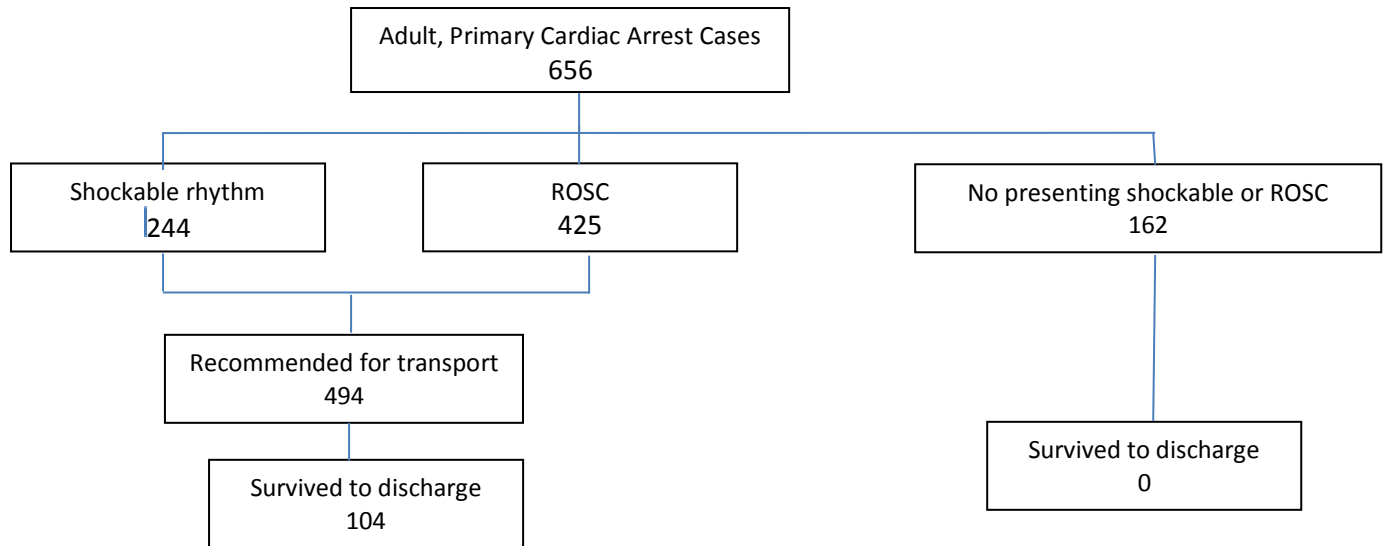
The TOR CDR recommended termination for 162 (24.7%) and transportation for 494 (75.3%) of the patients currently transported into hospital. Of the 162 patients that the TOR CDR recommended termination, none survived to hospital discharge. All 104 survivors in this phase of the study were recommended for transport by the



CDR. This equates to a positive predictive value of 100% (95%CI; 97.1% to 100%), specificity of 100% (95% CI: 95.6% to 100%), a negative predictive value of 21.1% (95%CI; 17.6% to 25.0%), and a sensitivity of 29.3% (95% CI: 25.6% to 33.4%). The transportation rate indicated during the prospective validation was 75.3%.



**Figure 11 – Prospective validation - Disposition of cardiac arrest patients**



**Figure 12 - Prospective validation - results**

Observed	TOR CDR	
	Transport	Terminate
<b>Died</b>	<b>390</b>	<b>162</b>
<b>% within CDR</b>	<b>78.9%</b>	<b>100%</b>
<b>% of total</b>	<b>59.5%</b>	<b>24.7%</b>
<b>Survived</b>	<b>104</b>	<b>0</b>
<b>% within CDR</b>	<b>21.1%</b>	<b>0.0%</b>
<b>% of total</b>	<b>15.9%</b>	<b>0.0%</b>
<b>Total</b>	<b>494</b>	<b>162</b>

**Table 16 - Prospective validation – table of results**

## 7.6 Comparison with other CDRs

In order to determine how the CDR fared when compared with existing CDRs, the BLS and ALS CDRs were applied to the data. Applying the BLS TOR to the dataset resulted in 570 patients being recommended for transport, 104 (18.2%) of whom survived. 85 (13.0%) patients were recommended for termination, and none

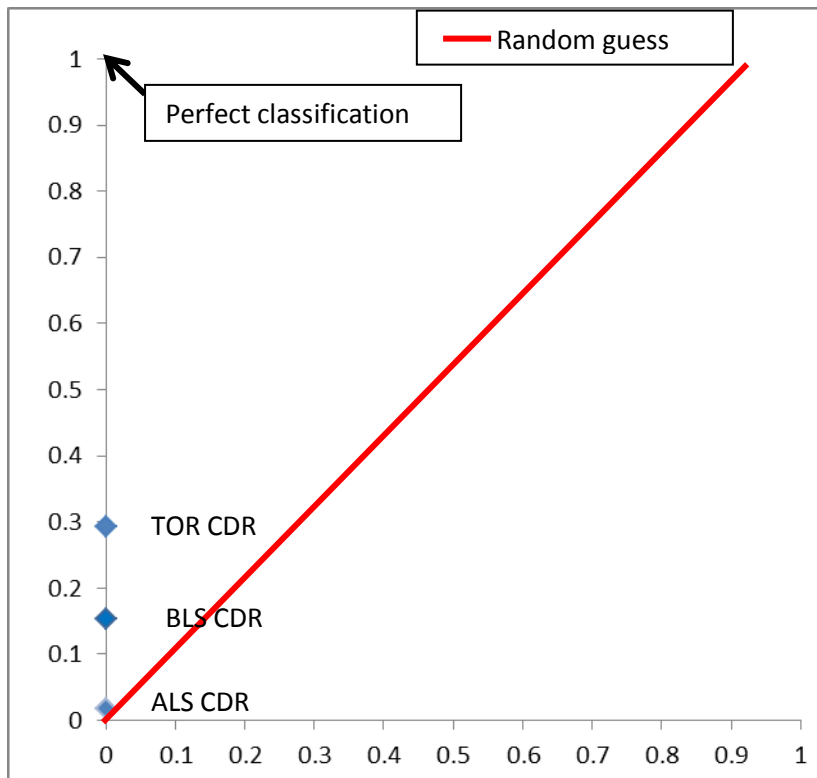
survived. This equates to a specificity of 100% (95% CI: 95.6% to 100%), a positive predictive value of 100% (95% CI: 94.6% to 100%), sensitivity of 15.4% (95% CI: 12.6% to 18.8%) and a negative predictive value of 18.2% (95% CI: 15.2% to 21.7%). This would have resulted in a transport rate of 87.0%.

Applying the ALS TOR criteria to the dataset resulted in 10 patients recommended for termination; with none of these surviving. 645 (98.2%) patients were recommended for transport. Of these 104 (16.1%) survived. This equates to a specificity of 100% (95% CI: 95.6% to 100%); a positive predictive value of 100% (95% CI: 65.5% to 100%); sensitivity of 1.8% (95% CI: 0.9% to 3.4%); and a negative predictive value of 16.1% (95% CI: 13.4% to 19.2%). The transport rate, when applying this CDR is 98.2%. As in the previous phases of this study, these results show that the TOR CDR has the potential to reduce the number of futile transportations, when compared to either the BLS or ALS CDRs.

	TOR CDR	BLS CDR	ALS CDR
Specificity	100% (95% CI: 95.6% to 100%)	100% (95% CI: 95.6% to 100%)	100% (95% CI: 95.6% to 100%)
Sensitivity	29.3% (95% CI: 25.6% to 33.4%)	15.4% (95% CI: 12.6% to 18.8%)	1.8% (95% CI: 0.9% to 3.4%)
PPV	100% (95%CI; 97.1% to 100%)	100% (95% CI: 94.6% to 100%)	100% (95% CI: 65.5% to 100%)
NPV	21.1% (95%CI; 17.6% to 25.0%)	18.2% (95% CI: 15.2% to 21.7%)	16.1% (95% CI: 13.4% to 19.2%)
Transport rate	75.3%	87.0%	98.2%

**Table 17 – Characteristics of CDRs in phase 3**

As with previous phases of this study, when plotted on a ROC space (Figure 13), the TOR CDR shows the best predictive power, when compared to either the BLS CDR or the ALS CDR.



**Figure 13 – ROC space comparing three CDRs**

## 7.7 Discussion

The aim of this phase of the thesis was to validate prospectively the CDR, to ensure that ambulance clinicians are able to apply the TOR CDR and identify those patients for who transport to hospital is futile. It has already been discussed how the issue of TOR in OHCA is complex and requires the balance between the need to achieve survival wherever possible against the unnecessary use of limited medical resources for transporting patients to hospital who have no chance of survival. Despite the potential complexities, any rule aimed at achieving this must be useable by ambulance clinicians in the field, where decisions need to be made quickly and with limited availability of senior clinical advice. As previously discussed, various TOR guidelines for OHCA have been validated and implemented in several Countries<sup>203</sup>,<sup>204</sup>,<sup>205</sup>. However, these guidelines were produced for different EMS systems and models. Whilst current practice within the Trust allows for TOR in very limited

circumstances, large numbers of patients are transported to hospital, the majority of who do not go on to survive the event. This phase has prospectively validated a TOR CDR that can be applied successfully by ambulance clinicians to that subset of patients currently required to be transported. It recommends termination for adult patients suffering OHCA of presumed cardiac aetiology who neither presented in a shockable rhythm nor achieved ROSC before transport. Of the 162 patients for whom the prediction rule recommended TOR, none survived to hospital discharge. The TOR CDR therefore successfully identified patients with OHCA for who transport was ultimately futile. However, the increase in the percentage of reported primary shockable rhythms when compared to previous phases (64.8% vs 36.5% and 47.1% respectively) as well as an increase in reported ROSC (64.8% vs 36.5% and 47.1% respectively) resulted in a higher than expected transport rate (74.6% vs 41.5% and 60.7% respectively). However, along with the increase in recommended transportation, there was also an increase in the proportion of survivors within the entire patient group when compared to previous phases (15.9% vs 10.6% and 15.4% respectively). The proportion of survivors within those recommended for transport increased from the phase 1 figure of 20.3% to 21.1%, although this was lower than that of phase 2 (25.6%).

Despite having prospectively validated the TOR CDR during this phase of the study, there are some caveats that must be mentioned. Firstly, as part of this study, the completion of TOR CDR forms was not mandatory. Forms were completed voluntarily by ambulance clinicians. There was an extensive information campaign as well as the enrolment of senior clinicians and other advocates to assist with the data gathering and the retrieval of missing data. Nevertheless, not all OHCA events were captured by this study over the course of the study period. Subsequent audit by

the Trust indicates that 1122 OHCA events were transported to hospital during the study period, of which 1080 were for patients 18 years of age or over; 935 were of presumed cardiac aetiology; and 669 had outcome data available. This equates to the capture of 98% of all possible events for this phase. Although this is high, there is the possibility that all of the missing events were survivors who fulfilled the TOR criteria. This leads to the second caveat, which is one of selection bias. There is the possibility that clinicians chose not to complete forms that did not appear to result in the perceived 'correct' outcome for the patient. The researcher has no evidence that this is the case, but is aware that this is a possibility. This may account for the previously discussed increase in transportation rate from this phase (74.6%), which is markedly higher than those of both the derivation phase (41.5%) and the retrospective validation phase (60.7%). As noted before, this increase is due to both an increase in the reported number of primary shockable rhythms (37.2% vs 28.4% and 32.9% respectively) as well as an increase in reported ROSC (64.8% vs 36.5% and 47.1% respectively). It should be noted, however, that the data used for the previous phases, as collected by the Trust record "ROSC at any time" and "ROSC at hospital". It was pointed out in Chapter 5 that for the purposes of the derivation and retrospective validation phases, these figures were combined, in order to capture all patients with ROSC. For this phase of the study the question asked clinicians "Was ROSC achieved before transport?" This difference in question may be the cause for the variation, though selection bias by individual clinicians cannot be ruled out at this stage.

Finally, there is the possibility that the awareness of this study may have affected the actions of clinicians on scene. Ultimately, the decision as to whether or not to transport a patient to hospital following OHCA lies with the clinicians on scene.

Despite policies, procedures and guidelines that attempt to regulate behaviour, compliance with these cannot be guaranteed in all circumstances. Therefore it is possible that when clinicians were making decisions at the time of the event, that their decisions were affected by CDR, despite the explicit direction on both the data-gathering documentation and the various awareness media that this should not be the case.

Having identified, and being aware of the potential limitations of this phase of the study, further work was done to determine whether the CDR could be improved using the prospectively captured data. It was therefore decided first to establish whether either primary shockable rhythm or ROSC could have been used alone as a CDR for TOR. This phase of the study was not intended for this purpose, but it was seen as appropriate, due to the increased incidence of both ROSC and primary shockable rhythm within the cohort. Both were therefore independently assessed for association with outcome using the Pearson's chi-square test. There was an association between initial shockable rhythm and survival, as expected:  $\chi^2(1) = 96.071$ .  $p < .001$ . However, as a single predictor, this would have resulted in 21 (5.1%) unexpected survivors. ROSC is considered to have the strongest association with survival <sup>112</sup>. In this sample, the association was confirmed:  $\chi^2(1) = 63.292$ ,  $p < .001$ . However, as a single predictor, this would have resulted in 1 (0.4%) unexpected survival. This is below the previously discussed definition of futility and could, in this sample, have been used as a predictor of survival. However, the inclusion of initial shockable rhythm improves both the positive predictive value and specificity of the CDR in this sample, by capturing that single survivor.

The increase in initial shockable rhythm and achievement of ROSC may be due selection bias, as noted above. However, the increase in ROSC may also be due to

the change in operational systems that were discussed in phase 2. During phase 3, 461 (64.8%) incidents had a minimum of four clinicians on scene during the resuscitation attempt. During phase 2, only 22% of incidents were attended by four or more clinicians, and whilst crew numbers were not recorded for the majority of incidents at phase 1, of the 981 cases where these data were recorded, 134 (13.6%) were attended by 4 or more clinicians. The RC(UK) recommend that a minimum of four trained staff are required to deliver high quality resuscitation for OHCA<sup>4</sup>. This was examined further by performing a Pearson's chi-square test to determine whether there was a relationship between the number of clinicians and survival. As one of the assumptions of the chi-square test is that the expected frequencies should be greater than 5, and this assumption was not met in all cases, the numbers were combined to include less than four and four or more clinicians. These groups were compared against both ROSC and survival, to determine if there is a significant association with either outcome. There was a significant association between the number of clinicians being four or more, and survival ( $\chi^2(1) = 8.964$ ,  $p = .003$ ). However, this appears to represent the fact that based on the odds ratio, fewer than four clinicians were 1.9 times more likely to result in survival. Although at first this appears counter-intuitive, it is perhaps not unexpected. One would expect patients who are more likely to survive an OHCA to achieve ROSC early in the resuscitation process. The consensus is that the patient group most likely to survive from an OHCA are those patients having a VF arrest, and who are defibrillated early<sup>27</sup>. Therefore, provided a single response with the ability to defibrillate arrives in a timely manner to these patients then, at least in theory, and provided ROSC is achieved, further resources may not be required on scene, as the patient is no longer in



cardiac arrest. So, it is only in the more difficult arrest scenarios, which have a reduced chance of success that extra resources will arrive on scene.

Similarly, it may be hypothesised that the attendance of a senior clinician at an OHCA may improve the chances of survival, as there is the assumption that this group of clinicians bring with them some advanced skills, as well as experience and improved clinical decision making. However, there was no significant association between the attendance of a senior clinician (either a Senior or Advanced Paramedic) and ROSC (  $\chi^2(1) = .252$ ,  $p = .616$ , or survival  $\chi^2(1) = .009$ ,  $p = .923$ ). Whether this was due to the selection bias mentioned earlier, or the result of some other factor is of interest and worthy of further study. However, it is beyond the scope of this thesis to look into this further.

The purpose of phase 3 was to complete the fourth objective of this thesis. That was, to validate prospectively the clinical decision rule, to ensure that ambulance clinicians are able to apply the TOR CDR and identify those patients for whom transport to hospital is futile. This sample of 656 cases has shown that ambulance clinicians are able to apply the TOR CDR and in doing so have identified patients who would not benefit from transport to hospital, with a positive predictive value and specificity of 100%. However, while this study has successfully validated the TOR CDR, it must also be recognised that these conclusions remain valid only as long as resuscitation practice and procedures within the Trust and the wider healthcare system remain consistent. If radically different procedures or techniques are introduced, then the TOR CDR would need to be re-considered against these. Although the high-impact initiatives such as quick response and early defibrillation are seen as important for improved survival, novel treatments and procedures may affect success rates for OHCA in such a way that those patients, for whom continued

resuscitation is presently considered futile, become potential survivors. In recent years, for example, it was thought that that therapeutic hypothermia may have been such a treatment <sup>206,207</sup>. Although subsequent work has suggested that this is not the silver bullet resuscitation practitioners have been looking for, the use of targeted temperature management has become part of the recommended treatment for post cardiac arrest patients <sup>27</sup>. Also, procedures such as percutaneous coronary intervention and extracorporeal membrane oxygenation during cardiac arrest may see positive results <sup>208</sup>. The latter is a technique whereby blood is diverted from the heart and artificially oxygenated outside of the body, allowing for CPR to be stopped, and other therapeutic techniques to be employed. Percutaneous coronary intervention is a technique used to open occluded blood vessels around the heart. Although these techniques were not in place at the time of this study, that is not to say that in time the same or different procedures will not require a revalidation of all existing TOR CDRs, including this one.

Similarly, recent work has suggested that futile resuscitations may be determined by use of end tidal capnometry (ETCO<sub>2</sub>). ETCO<sub>2</sub> measures the partial pressure of carbon dioxide at the end of an exhaled breath. It is an indication of both the patient's cardiac output and their pulmonary blood flow, as carbon dioxide is transported to the right atrium of the heart and then to the lungs by the right ventricle. Currently, ETCO<sub>2</sub> is used by Paramedics to determine correct placement of endotracheal tubes in the trachea <sup>60</sup>, and as a result of this, is a tool available to all pre-hospital clinicians who perform advanced airway techniques. Ahrens, Schallom, Bettorf *et al* found that in 127 patients, all but one with ETCO<sub>2</sub> of less than 10 mmHg died before discharge <sup>131</sup>. This is supported by the recent work of Ozturk, Parlak, Yolcu *et al* has suggested that if ETCO<sub>2</sub> remains under 10 mmHg during CPR, it is

likely that ROSC will not occur <sup>130</sup>. However, this study was small (n = 50), and there was one patient who survived, despite ETCO<sub>2</sub> of under 5 mmHg. ILCOR considered the prognostic value of ETCO<sub>2</sub> and recommended against using ETCO<sub>2</sub> cut-off values alone as a predictor of mortality or for deciding when to terminate a resuscitation attempt <sup>209</sup>. Nevertheless, developments in this area may prove the prognostic value of ETCO<sub>2</sub>, and may therefore affect the efficacy of any pre-existing TOR CDR.

Another area of study which may affect TOR decisions is the use of ultrasound as a prognostic tool. A review of the literature by Brooke, Walton, Scutt, *et al* found that there was evidence that with the right education, paramedic cohorts could be taught to use and interpret the results of ultrasound in the prehospital environment <sup>210</sup>. Further work by the same team found that advanced paramedics could acquire the knowledge and skills over a two-day course to acquire diagnostic quality ultrasound images to identify the presence or absence of pneumothoraces <sup>211</sup>. Although no studies could be found to indicate that paramedics are able to use ultrasound to assist with decisions on TOR, it is possible that protocols could be established for the assessment of myocardial contractility for presumed PEA, and so incorporated into a TOR CDR. The current expense of the equipment probably prohibits its introduction to all front-line clinicians at the present time, but there is some potential for future on-scene decision-making by senior paramedic clinicians.

As well as the impact of specific procedures to any TOR CDR, it is important to recognise organisational changes that may affect their validity. Work by Schober, Holzer, Hochrieser, *et al*. has found variation in survival between hospitals, which raises the question as to whether specialist resuscitation hospitals may result in

improved outcomes <sup>212</sup>. System changes such as this would require wholesale re-evaluation of pre-hospital TOR.

Nevertheless, until further work is progressed on novel treatments and procedures such as those mentioned, the validity of TOR CDRs based on the characteristics of the cardiac arrest remain valid. This validation has shown that paramedic clinicians are able to utilise a CDR that accurately identifies those patients for who transport to ED is futile. In order for this to be put into practice, however, it would need to be combined with the existing TOR guidelines to ensure that clinicians understood how the two elements interact, as well as ensuring that aggressive resuscitation is continued up until the point it is decided to terminate the attempt. Such guidance would need to include a minimum interval for which the attempt should be continued, as well as ensuring any reversible causes are addressed before a decision is made.

Having prospectively validated the CDR, the next chapter attempts to determine the economic impact of this decision-making on the ambulance service and the wider health economy.

## **8. Chapter eight – Estimate of cost savings**

Previous chapters have reported on a retrospective cohort study that derived a TOR CDR. They then reported on the subsequent retrospective and prospective cohort studies that validated this CDR. At each stage the results of this CDR were compared with the previously derived BLS and ALS CDRs to evaluate its effectiveness at recognising futile transportation following adult OHCA of suspected cardiac aetiology.

The aim of this chapter is to compare the costs to the NHS of introducing the various CDRs against current practice. As discussed previously, the NHS is under pressure to reduce spending, whilst improving standards and efficiency <sup>188</sup>. This relentless pressure to deliver more and better healthcare for less understandably means there is an emphasis on establishing ways to reduce expenditure. Early decisions, which reduce the need for unnecessary, futile care are in great demand. Previous chapters have shown that the TOR CDR can effectively identify futile transportation and that clinicians are able to use the CDR in practice. If the application of the CDR can be shown also to have positive financial implications, then the case for introducing it is strengthened. Although only explicit cost will be considered here, it is anticipated that there will be resource and cost implications for the Trust and the wider healthcare economy, which are implicit and cannot easily be measured. They include the availability of the transporting ambulances to attend other emergency calls, and the attending staff at hospital being able to concentrate on other patients and tasks. However, these effects are beyond the scope of this thesis and further research would be needed to quantify them.

## 8.1 Literature search

Before estimating the cost savings, a literature search was performed to determine if evidence existed on the cost of TOR for adult OHCA patients in the field and in hospital. It was found that there is limited evidence available that addresses the cost of OHCA in the UK. Furthermore, difficulties in quantifying the cost of these futile transports are evident in the literature. In 1993, Bonnin, Pepe, Kimball *et al* estimated that transporting patients to the hospital for “continued but futile” resuscitation cost between \$2000 to \$3000 per patient <sup>126</sup>. In 2000, Cheung, Morrison and Verbeek compared the costs of TOR in the pre-hospital environment to the costs of transporting patients to hospital for TOR in a single Canadian hospital <sup>213</sup>. They analysed data from 20 patients subject to TOR by ambulance staff and matched these to 20 patients subject to TOR in the ED. They found that the total cost of TOR in the ED was \$45.35 higher than the cost of TOR in the field ( $p < 0.001$ ), with Paramedic TOR costing approximately \$159.41 against hospital TOR costing \$204.76 overall.

However, in addition to ambulance costs, the greatest costs are associated with hospital interventions, particularly when patients survive long enough to be transferred to intensive care units (ICU). The data available at the time of writing does not allow a detailed analysis of these costs, but they nevertheless become important to the overall cost of treating OHCA. In order to make an overall assessment of the cost impact to the NHS of introducing a prehospital TOR CDR, ideally the hospital costs of treatment leading to the discharge of survivors as well as costs relating to non-survivors must be taken into account.

In 1991 Gray, Capone and Most evaluated the costs of continued hospital resuscitation for 185 patients suffering OHCA and transported to a Rhode Island

hospital, of whom 16 (9%) survived to admission from ED, and none survived to discharge<sup>214</sup>. They concluded that the mean stay in hospital for the 16 patients who survived to be admitted from ED was 12.6 days, with a mean stay in ICU of 2.3 days. This resulted in a cost of hospitalisation of \$180,908, with a mean cost per patient of \$11,307.

In 1996 Dhar, Ostryzniuk, Roberts *et al* retrospectively reviewed 285 consecutive admissions to a university hospital ICU following resuscitation to determine long-term outcome, length of stay, and resource consumption<sup>215</sup>. This study involved both in-hospital and OHCA patients and not all patients suffered an arrest of cardiac origin, so these results may not be generalised to a purely OHCA cohort who suffered an arrest of cardiac aetiology. However, they found that overall the 94 survivors spent a total of 2589 hospital days in hospital, whereas the 191 non-survivors spent 1076 days in hospital. The non-survivors had statistically higher ( $p < 0.01$ ) mean and median daily costs in ICU (mean \$175; median \$143) than survivors (mean \$145; median \$140).

Swor, Lucia, McQueen *et al* compared the cost of treating OHCA patients with patients treated with ST-segment acute myocardial infarction (heart attack)<sup>216</sup>. This work, from 2010 in USA, suggests that the median length of stay in hospital of all OHCA patients was 4 days. The study however looked only at patients who survived OHCA to discharge, and even then may have excluded those who were resuscitated fully in the prehospital phase and entered the hospital without on-going resuscitation. Due to the methods employed in this study, and its emphasis on revenue gained from each patient encounter, any costs it concluded cannot be generalised to the UK system.

In 2002, Gage, Kenward, Hodgetts *et al* reported on health system resources used to treat OHCA in a British district general hospital, following a prospective observational study <sup>217</sup>. They found that based on costs for the financial year 1999-2000, the average variable cost per resuscitation attempt was £195.66. The mean fixed cost per resuscitation attempt, which included provision and maintenance of capital equipment, and the training of clinicians in resuscitation skills, was £928.81. They calculated an overall average cost of £1165.48 per resuscitation attempt, and £8278.65 per survivor, where the survival rate was 13.6%.

Naess and Steen studied long-term survival and estimated the costs per year of survival after OHCA of cardiac origin, treated by an ambulance, staffed by a doctor, in Oslo from January 1971 to June 1992 <sup>218</sup>. During this study 9.5% of patients with OHCA of cardiac origin and who had fully available documentation survived to discharge. They included costs of EMS, hospital treatment, rehabilitation, nursing homes and psychiatric institutions after discharge. They concluded that the cost per patient discharged alive was €40,642 or €6,632 per life year gained, with 4.4% of the total costs being spent on patients who did not survive to hospital, 35.6% on patients who died in hospital and 60% on those who were discharged from hospital alive. This study highlights the difference in costs between prehospital TOR and in-hospital TOR. However, whilst 57.6% of resuscitations were terminated before ROSC (combined pre-hospital and ED TOR), there is no indication of how many of these patients were actually transported to ED.

The costs of ICU stays for patients suffering OHCA were again studied by Graf, Mühlhoff, Doig *et al* in 2008 <sup>219</sup>. This study was aimed at investigating the cost per life-year gained from data gathered at a single German ICU for any patient suffering OHCA, whatever the cause. It nevertheless established the cost per survivor, by



dividing the total healthcare costs (including ICU, hospital and post-hospital discharge) by the number of patients who survived to hospital discharge. The costs per hospital survivor were found to be €49,952 (total hospital costs = €7,492,771, divided by 150 hospital discharge survivors). Although specific costs were attributed to each individual patient in this study, these are not individually quantified in the final analysis. Therefore, whilst this study is of interest, it does not relate purely to OHCA of cardiac aetiology and so cannot be generalised to this group of patients specifically.

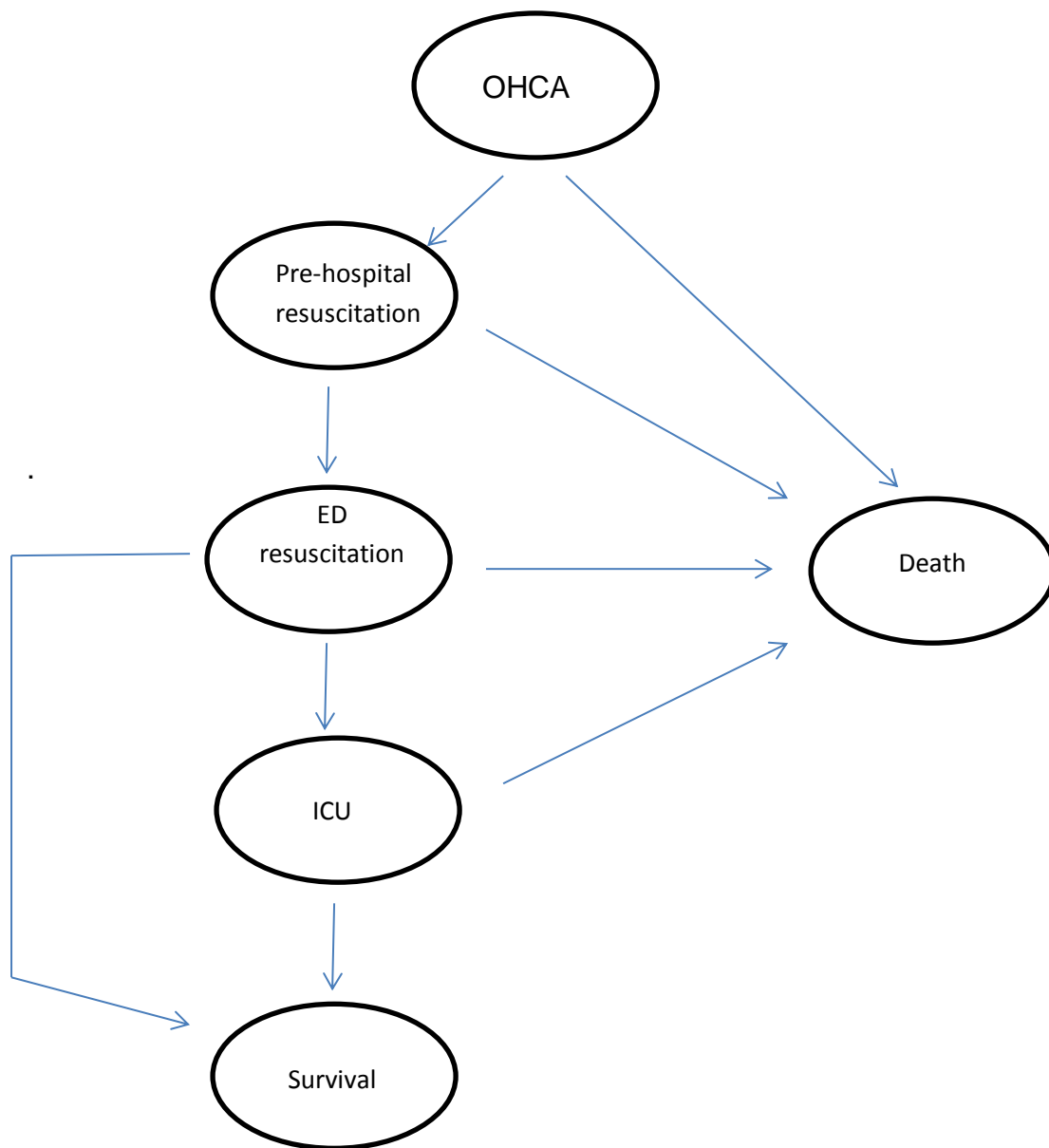
The most recent study by Petrie, Easton, Naik *et al* in 2015 was a single centre retrospective review of in-hospital costs of patients admitted to the ICU following ROSC after OHCA <sup>220</sup>. This study reviewed successive patients admitted over an 18-month period, and established costs, which were defined as the sum of money allocated to each patient episode, as generated using the UK payment by results (PbR) system. This methodology was comprehensive and accounted for hotel services, medical, nursing and other clinical staff costs, treatments, ward consumables, medicines, blood and blood products, medical and surgical equipment, and any diagnostics undertaken while the patient was in the ICU. A total of 68 patients who required ICU admission following OHCA were included in the study. A further 101 OHCA patients were excluded as they were not admitted to ICU. This study found that the average overall hospital cost per patient, including non-survivors admitted to ICU was £20,000. The overall hospital cost per survivor was £51,000 (£1,698,000/33). The cost per ICU day was calculated to be £1700. Although this study reviewed all OHCA patients, irrespective of aetiology, the majority (78%) of arrests were of cardiac origin. In contrast to the previously mentioned studies, this study utilises reasonably current data from 2011–2012, and

includes the latest treatments for cardiac arrest patients, including targeted temperature management and primary percutaneous intervention. Inevitably, there are time dependant inflationary changes and other economic factors, such as variations in purchasing power, which mean the figures quoted here will not correlate exactly to the costs relating to the patient group of interest to this thesis. Moreover, the treatment options for patients will vary depending on the receiving hospital. However, as the most recent and thorough UK study, it does give a good indication of the costs involved.

## **8.2 Methods**

In order to estimate the cost savings of the three service options (TOR CDR; BLS CDR; and ALS CDR) against current practice, a retrospective review of the patients from phase 3 who were eligible for TOR under each of the CDRs, was conducted. This was done in order to identify and compare the costs of each CDR with those of current practice, where all of the patients are transported to hospital and TOR occurs there. The analysis was performed from an acute care perspective, determining only those costs associated with treatment up to the point of TOR. The aim was to determine the cost savings from adult OHCA of cardiac aetiology, as a result of early TOR for non-survivors. It was hypothesised that prehospital TOR would be associated with lower costs than transport and TOR in hospital and that the CDR established in this thesis would be associated with lower costs than either the BLS or ALS CDRs.

To establish the cost of interventions, first the patient pathways associated with OHCA were established (Figure 14).



**Figure 14 - Schematic diagram of patient pathways**

Patients all enter the pathway as OHCA. On arrival of the ambulance, they may be diagnosed as dead at this point, or resuscitation may be attempted. If attempted, the resuscitation may be terminated on scene, or the patient is transported to ED. Once in ED, the resuscitation attempt may be terminated, or continued. The schematic shows that the stage at which the patient is resuscitated successfully may vary (though this is not affected by the CDR). If resuscitated in the pre-hospital

environment, the patient will still require transport to the ED, though this may not necessitate ICU admission. Similarly, successful resuscitation in the ED may, or may not require ICU admission. The end-state for patients within this pathway is not changed by the implementation of any of the CDRs: patient survival is not affected by the application of the CDR. However; the stage at which patients are identified as being irreversibly dead is affected. This stage may either be by ambulance clinicians in the pre-hospital phase; by emergency physicians in the ED; or by intensivists in the ICU.

### **8.3 Estimation of costs used within the model**

The prospective cohort study used to validate the CDR consisted of 656 patients. Of these, the TOR CDR recommended prehospital TOR for 162 patients. The approach taken was to look at the reduction in cost that would result from the implementation of each of the CDRs, by calculating estimated costs for each non-survivor that was transported to ED and then estimating the effect on that cost under the newly-established CDR as well as under the BLS and ALS CDRs.

In order to complete an estimate of cost savings, relevant costs needed to be established, or assumed. For each patient, only limited data were available from the Trust's records: number of clinicians on scene; treatment interval; travel interval; survival outcome; and if the patient died, whether this was before or after 24 hours. Several assumptions therefore needed to be made in terms of treatment and the costs of that treatment. The approach taken here was to minimise the assumed costs for both the ambulance and subsequent hospital treatment for all patients. In that way, any savings as a result of implementing the CDR will not be over-estimated.

The first assumptions are in terms of ambulance costs. It was assumed that all ambulance interventions on scene would not be affected by implementing the CDR. All ALS procedures would be performed according to RC(UK) guidelines, whether or not the CDRs are used, and so use of equipment and medicines were presumed to be equivalent throughout. It was therefore assumed that no extra costs for equipment or medicines were incurred by the ambulance Trust when transporting a patient to hospital.

Once a crew has completed at an incident, that crew must spend time completing paperwork, re-packing response bags from their vehicle stocks, debriefing the incident etc. It was assumed that whether this is done on scene or at hospital, the time spent doing this would be equivalent throughout. Leading on from those previous assumptions, the only added expense is the time spent in transit with the patient. These data were available as a travel interval for each incident.

Although there may have been more than one ambulance on scene, it was assumed that during transport, only a single crew (two clinicians) attended the patient; one to drive and the other to treat the patient. It was therefore assumed that any other clinicians remain at scene and are available for further incidents. Although this is not always the case, and a second attending clinician may travel with the patient in the ambulance, this assumption was again made so as not to over-estimate any cost implications of implementing the CDRs.

The only data available relating to hospital expenditure was whether the patient survived and, if they died, whether this occurred before or after 24 hours. Again several assumptions needed to be made here. Firstly, it was assumed that if the patient survived less than 24 hours, that they were taken into ED and that twenty

minutes of ALS was performed before resuscitation was terminated. It is accepted that on occasion, the attempt may be terminated almost upon arrival at ED, once the attending doctor has been told the details of the arrest, the intervals involved and the treatment already provided. Alternatively, other patients may achieve ROSC and require further interventions. However, it is reasonable to assume that for the majority of patients, twenty minutes of ALS is performed before termination in the ED. Further assumptions needed to be made in terms of attending staff at the hospital. All EDs to which OHCA's are taken receive a pre-alert from the Trust. This pre-alert is a telephone call that gives brief details of the patient, the history of the incident and treatment provided, as well as an estimated time of arrival at the ED. Therefore it can be assumed that the ED would have a minimum clinical response available for each OHCA. This was assumed to be one ED registrar, one anaesthetics registrar and two band 5 nurses. This assumption is based on the need for at least two persons to continue CPR, an ED lead and an airway management specialist. Although there is the potential for more, or higher grade staff to be in attendance, these numbers and grades were again used so as not to over-estimate costs.

If a patient was known to have survived over 24 hours, it was assumed that they were taken to intensive care. As the actual length of stay in intensive was not available, each intensive care stay was assumed to have been no longer than 24 hours for this analysis. Again, this assumption ensured that there was no exaggeration of hospital costs. In fact, they may greatly underestimate costs. However, it was decided that a large underestimation of cost benefit of introducing a CDR was preferential to even a small overestimation of that benefit, so as not to unreasonably raise expectation.

The Personal Social Services Research Unit publishes figures on the estimated unit costs of NHS staff and services <sup>221</sup>. These data were used to calculate costs of ED staff (registrar = £41 per hour; Band 5 nurse = £35 per hour). However, whilst this data estimates the costs of ambulance attendances, these are calculated per incident and are not calculated per hour. Therefore Trust data was used to calculate the cost of travel intervals. The Trust currently equates the cost of a double crewed ambulance to £72 per hour (np- see appendix 7) (This value is specific to the Trust and may not equate to all ambulance trusts throughout the UK). For ICU costs, the work of Petrie, Easton, Naikcost *et al* was used. This work calculated that the cost per ICU day for a patient following cardiac arrest was £1700 <sup>220</sup>.

<b>Costs</b>	<b>Value (2015)</b>	<b>Source</b>
Double crewed ambulance	£72 per hour	Trust data (np – see appendix 7)
ED registrar	£41 per hour	Personal Social Services Research Unit <sup>221</sup>
Anaesthetic registrar	£41 per hour	Personal Social Services Research Unit <sup>221</sup>
Band 5 nurse	£35 per hour	Personal Social Services Research Unit <sup>221</sup>
ICU	£1700 per day	Petrie, Easton, Naikcost <i>et al</i> <sup>220</sup>

**Table 18 – Costs used in the model**

## 8.4 Results

This section reports the results of the costs for the three alternative termination rules that have been identified, compared with current practice.

A cost identification analysis was first performed on existing processes. 737 patients were transported to hospital during phase 3. Of these, survival data was available for 656 patients. The total travel interval for these patients was 120 hours 53 minutes. However, of these, 104 survived, accounting for 25 hours of travel. Therefore 95 hours and 53 minutes of travel was spent on non-survivors. Of the 552 non-survivors, 454 died within 24 hours, and 98 died over 24 hours after arrival.

Number of Patients	Intervention	Unit Cost	Total cost
552	transport	£72 per hour	£6,903.6
552	2 x Registrar	£41 per hour each	£15,088
552	2 x Band 5 nurse	£35 per hour each	£12,880
98	ICU	£1,700 per 24 hours	£166,600
			<b>£201,471.6</b>

**Table 19 – Cost identification of current processes**

A cost identification analysis was then performed on the results of the phase 3 TOR CDR figures, as if those patients recommended for TOR had not been transported to ED.

Applying the TOR CDR to the patients for whom outcome is known, would have resulted in 494 patients being transported to hospital during phase 3. The total travel interval for these patients was 92 hours 47 minutes. However, of these, 104 survived, accounting for 25 hours of travel. Therefore 67 hours and 47 minutes of travel was spent on non-survivors. Of the 390 non-survivors, 299 died within 24 hours, and 91 died over 24 hours after arrival.

Number of Patients	Intervention	Unit Cost	Total cost
390	transport	£72 per hour	£4,880.4
390	2 x Registrar	£41 per hour each	£10,659.18
390	2 x Band 5 nurse	£35 per hour each	£9,099.3
91	ICU	£1,700 per 24 hours	£154,700
			<b>£179,338.88</b>

**Table 20 – Cost identification of TOR CDR**

Applying the BLS CDR to the patients for whom outcome is known, would have resulted in 570 patients being transported to hospital during phase 3. The total travel interval for these patients was 107 hours 3 minutes. Removing the 104 survivors (25 hours of travel), leaves 82 hours and 3 minutes of travel spent on non-survivors. Of



the 466 non-survivors, 371 died within 24 hours, and 95 died over 24 hours after arrival.

Number of	Intervention	Unit Cost	Total cost
466	transport	£72 per hour	£5,907.6
466	2 x Registrar	£41 per hour each	£12,737.88
466	2 x Band 5 nurse	£35 per hour each	£10,873.8
95	ICU	£1,700 per 24 hrs	£161,500
			<b>£191,019.28</b>

**Table 21 – Cost identification of BLS CDR**

Applying the ALS CDR to the patients for whom outcome is known, would have resulted in 645 patients being transported to hospital during phase 3. The total travel interval for these patients was 119 hours 10 minutes. Removing the 104 survivors (25 hours of travel), leaves 94 hours and 10 minutes of travel spent on non-survivors. The total cost of this transfer interval (@ £72 per hour) is therefore £6,768

Of the 541 non-survivors, 443 died within 24 hours, and 98 died over 24 hours after arrival.

Number of	Intervention	Unit Cost	Total cost
541	transport	£72 per hour	£6,768
541	2 x Registrar	£41 per hour each	£14,787.88
541	2 x Band 5 nurse	£35 per hour each	£12,623.8
98	ICU	£1,700 per 24 hrs	£166,600
			<b>£200,779.68</b>

**Table 22 – Cost identification of ALS CDR**

From the costings above, it is possible to establish the total additional cost per non-survivor, by dividing the total cost by the number of patients who did not survive to discharge (including those terminated on scene). The total saving per 1,000 patients currently transported to hospital can then be calculated (Table 23).

Clinical Decision Rule	Cost	Cost per patient	Cost per 1000 patients	Cost-saving per 1000 patients
Present position	£201,471.6	£307.12	£307,121	
TOR CDR	£179,338.88	£273.38	£273,382	<b>£33,739</b>
BLS CDR	£191,019.28	£291.19	£291,188	<b>£15,933</b>
ALS TOR	£200,779.68	£306.07	£306,067	<b>£1,054</b>

**Table 23 – Total cost savings per 1,000 patients currently transported**

## 8.5 Discussion

Utilising the figures above, the current minimum cost of transporting 1,000 patients who do not survive is £307,121. Applying any of the three CDRs results in a reduction of cost: £1,054 for the ALS CDR; £15,933 for the BLS CDR; and £33,739 for the TOR CDR. Due to the assumptions that were made, this is the minimum saving. The calculation did not include any cost connected to time spent by ED staff in matters indirectly related the OHCA patient, such as time spent with members of the deceased's family, supporting any family members who may have attended the hospital, contacting the coroner, or the completion of documentation, removal of the deceased etc. Yet, all of these activities are important as they detract from the time available to ED staff to care for other patients. Nevertheless, this demonstrates that the TOR CDR has the potential to contribute to financial savings by conserving the limited resources available to the healthcare system, and the financial impact of this.

Also, the impact of transporting fewer patients to hospital cannot be quantified in terms of the effect on other patients attending that hospital at the same time. This impact may include the availability of staff, beds and other facilities that would otherwise be needed to treat the OHCA patient. Assumptions were made that four members of hospital staff would be required to attend each OHCA patient brought into the ward and would be attended for twenty minutes. As explained earlier, these figures are deliberately conservative. They do not account for the time spent waiting for an ambulance to arrive at ED once the hospital has been alerted that an OHCA is

expected on the ward, nor the time required for the appropriate staff to leave their current location to attend the ED. All of this removes hospital clinicians from their ongoing work, which will impact on other patients. Future evaluations should incorporate the impact of this resource allocation on the wider population.

The generalisability of any research findings are an important consideration. In order to assess this, one must consider not only the quality of research, but also its applicability to different health settings and their impact on different patient groups<sup>180</sup>. Although this study was conducted over a large geographical area, which includes both densely urbanised and sparsely rural areas, and also considered a large population base, there are certain elements that may affect its generalisability to other areas. Firstly, all the clinicians were from a single ambulance trust and were following the clinical guidelines of that trust, as well as the operational model of that trust, in relation to deployment models, use of senior clinicians etc. As was noted in earlier chapters, the increase in ROSC over the three phases of the study may have been influenced by the changes in operational model of the Trust. So too, different response models in other ambulance services may impact on the generalisability of these findings. Also, it was noted in chapter 2 that the incidence of VF arrests may be declining with time. If this trend continues, the number of patients eligible for pre-hospital TOR using the CDR may increase over time. Nevertheless, this estimate of cost savings suggests that the implementation any of the CDRs will have financial benefits when compared to current practice. Furthermore, the TOR CDR was shown to have greater financial benefits, when compared to either the BLS or ALS CDRs.

## 9. Chapter nine – Conclusion

The focus of this thesis was the pre-hospital termination of adult OHCA of presumed cardiac origin, and posed the question as to whether it is possible to predict when a patient suffering such an event would not benefit from transport to hospital, and the attempt terminated safely whilst minimising the possibility of stopping a potentially survivable resuscitation attempt.

It was established that CDRs have been validated that successfully identify patients suffering OHCA for whom transport to hospital would be futile. However, the numbers of patients transported to hospital using these CDRs are relatively high, and they are therefore potentially recommending transport for resuscitation attempts that are objectively futile. It was also noted that these rules were created for ambulance systems that at the time the CDRs were derived were not able to terminate asystolic OHCA. This meant they were intended for a larger subset of patients than those currently transported by the Trust in question.

A new TOR CDR was therefore derived by performing a retrospective cohort study using pre-existing data gathered from a single, large UK ambulance Trust over a 26 month period. The study evaluated 4870 individual OHCA. Binominal logistic regression was performed to determine the variables associated with outcome, defined as either death or survival to hospital discharge. This TOR CDR predicted that patients without an initial VF/pVT rhythm or ROSC on scene were unlikely to result in survival. Applying this TOR CDR to the patients in the original dataset resulted in a transport rate of 52.4% and 5 (0.2%) unexpected survivors. (specificity = 99.0%; 95% CI: 97.7% to 99.7%, positive predictive value = 99.8%; 95% CI: 99.5% to 99.9%, sensitivity = 53.1%, 95% CI: 51.6% to 54.6%, and negative predictive 20.3%, 95% CI: 19.8% to 20.9%). These results compared favourably to both the

BLS and ALS CDRs, which had transport rates of 63.1% and 90.2% respectively, although application of both of these CDRs resulted in fewer unexpected survivors (n=3 and n=2 respectively).

A subsequent retrospective cohort study of 2139 adult patients who had an OHCA of presumed cardiac aetiology resulted in a transport rate of 60.7%, with 3 (0.4%) unexpected survivors (specificity = 99.1%; 95% CI: 97.4% to 99.8%, positive predictive value = 99.6%; 95%CI; 99.0% to 99.9%, sensitivity = 46.5%; 95% CI: 44.1% to 48.8%, and negative predictive value = 25.6%; 95%CI; 23.2% to 28.1%. Again the BLS and ALS CDRs were applied to the same data. Although neither resulted in any unexpected survivors in this group of patients, the transport rates increased to 72.8% and 95.2% respectively.

A prospective validation of 656 patients showed resulted in 162 patients being recommended for TOR. None of these survived to hospital discharge. All of the 104 survivors in this phase of the study were recommended for transport by the CDR. (specificity = 100%; 95% CI: 95.6% to 100%; positive predictive value = 100%; 95%CI; 97.1% to 100%, sensitivity = 29.3%; 95% CI: 25.6% to 33.4%; negative predictive value = 21.1%; 95%CI; 17.6% to 25.0%). The transportation rate was 75.3% of those currently transported. Retrospective application of both the BLS and ALS CDRs to the same population showed that whilst both also identified 100% of survivors for transport, they did this with increased transport rates (87% and 98.2% respectively).

An estimate of the cost savings of introducing the TOR CDR into practice showed that all three CDRs would result in cost savings, as each resulted in fewer patients being transported to hospital. When extrapolated, the estimated cost savings per

1,000 patients currently transported to hospital were £33,739 for the TOR CDR, as opposed to £15,933 for the BLS CDR and £1,054 for the ALS CDR. It was also noted that there are other effects that cannot easily be quantified. These include the added benefit of releasing ambulance clinicians more quickly to attend the next emergency, or allowing hospital clinicians to attend other patients, rather than dealing with time-intensive, yet ultimately futile resuscitation attempts.

In completing these stages of the thesis, the following objectives were achieved: to evaluate critically the existing validations of clinical decision rules (CDRs) relating to termination of resuscitation; to derive a TOR CDR for adult OHCA of cardiac aetiology that is appropriate for use by pre-hospital clinicians, and which reduces the number of futile resuscitation attempts transported to hospital; to validate retrospectively the CDR against an independent data-set of out-of-hospital cardiac arrests; to validate prospectively the CDR, to ensure that ambulance clinicians are able to apply the TOR CDR and identify those patients for who transport to hospital is futile; to estimate the cost savings of introducing the TOR CDR.

Some of the strengths and limitations of this thesis have been discussed in previous chapters. The strength of the thesis is that it derived the elements of a CDR through the use of logistic regression, and clinical application of the results, and then proved the application of the CDR by both retrospective and prospective validation. However, as previously discussed, McGinn *et al* require that in order to achieve a level 1 in the hierarchy of CDRs, a guideline must have undergone at least one prospective validation in a different population to the derivation, and one impact analysis, as well as having demonstrated a change in clinician behaviour and beneficial consequences<sup>141</sup>. This study has not achieved this standard. In particular, because senior clinicians assisted with the collection of missing data in phase 3, it

cannot be said with certainty how much of the data was provided by front-line clinicians. Moreover, it cannot be said that the CDR demonstrated a change in clinical behaviour. Therefore, this study can be said to have reached the standard of a level 3 validation, which is one that has utilised only one narrow, prospective sample. Nevertheless, McGinn et al argue that level 3 validations can result in a decision rule being implemented <sup>141</sup>. Therefore, whilst this thesis has provided the evidence to introduce the CDR into the practice of the Trust, it cannot be generalised to other locations, or EMS systems. In order to strengthen the validity of the tool, it should be assessed prospectively in either one large prospective study or several smaller studies, but within different settings. Ideally, to prevent bias, such a validation would be performed by a different research group <sup>145</sup>.

It is recommended that further research should also look in more detail into the potential cost savings and other benefits of introducing this CDR. By necessity, the cost savings illustrated in this thesis were broad and generalised, aiming to provide an indication of the minimum savings associated with the introduction of the CDR. More detailed research into the costs of futile transportation, including the effects on availability of resources both in terms of ambulances and hospital clinicians is required.

Despite the limitations discussed throughout this thesis, it has nevertheless achieved the aims it has set out to achieve. It has shown that it is possible to reduce safely the number of futile, adult OHCA patients who are currently transported to hospital. The tool with which this can be done has been derived and validated both retrospectively and prospectively. It compares favourably with two existing decision rules, by identifying more futile transportations than either the BLS or ALS CDRs. The CDR is applicable to adult patients who have suffered an OHCA of presumed cardiac

aetiology and who would presently be transported to hospital. The rule states that if the patient did not present in a VF/pVT rhythm and did not achieve ROSC on scene, then it is futile to transport them to hospital for further resuscitation attempts, and the attempt can safely be terminated on scene. For these purposes, futility is defined as a probability of survival of less than one percent.



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## APPENDIX 1 – Search terms

Search completed January 2013:

### Initial Search

1. TOPIC: (resuscitation) AND TOPIC: ("out of hospital") AND TOPIC: (predict\*) AND TOPIC: (survival); 476 results

### Web of Science Search

# 16	77	#9 AND #6 <b>Refined by:</b> [excluding] <b>WEB OF SCIENCE CATEGORIES:</b> AND <b>DOCUMENT TYPES:</b> ( ARTICLE ) AND ( PEDIATRICS ) AND [excluding] <b>DOCUMENT TYPES:</b> ( PROCEEDINGS PAPER )
# 15	119	#9 AND #6 <b>Refined by:</b> [excluding] <b>WEB OF SCIENCE CATEGORIES:</b> ( PEDIATRICS )
# 14	11	#14 AND #6
# 13	42	#13 AND #9
# 12	280,942	<b>TOPIC:</b> (validation)
# 11	124	#9 AND #6
# 10	44	#9 AND #4
# 9	3,044	#3 AND #2
# 8	46	#7 AND #4
# 7	427	#6 AND #2
# 6	36,825	#5 OR #1
# 5	36,825	<b>TOPIC:</b> ((resuscitation))
# 4	5,093	<b>TOPIC:</b> ((futil*))
# 3	611,541	<b>TOPIC:</b> ((rule* OR guideline*))
# 2	132,325	<b>TOPIC:</b> ((terminat*))
# 1	13,609	<b>TOPIC:</b> (((cardiopulmonary resuscitation)))

## MEDLINE Search

# 8	24	((cardiopulmonary resuscitation OR resuscitation) AND (rule OR guideline)) AND terminat*).ti,ab
# 7	334	((cardiopulmonary resuscitation OR resuscitation) AND terminat*).ti,ab
# 6	28,204	(cardiopulmonary resuscitation OR resuscitation).ti,ab
# 5	28,204	(resuscitation).ti,ab
# 4	3,726	(futil*).ti,ab
# 3	261,106	(rule* OR guideline*).ti,ab
# 2	66,119	(terminat*).ti,ab
# 1	8,253	(cardiopulmonary resuscitation).ti,ab

## Appendix 2 - Results of literature search

Ser	First Author	Year	Title	Excluded by Title	Excluded by Abstract	Review
1	Ågård	2012	Guidance for ambulance personnel on decisions and situations related to out-of-hospital CPR.		✓	
2	Berdowski	2010	Chest Compressions Cause Recurrence of Ventricular Fibrillation After the First Successful Conversion by Defibrillation in Out-of-Hospital Cardiac Arrest	✓		
3	Birkholz	2009	End-of-life decision-taking in out-of-hospital resuscitation- abandonment of attempted resuscitation in a cancer patient, on the basis of a clinical guideline	✓		
4	Bjorshol	2011	Decay in chest compression quality due to fatigue is rare during prolonged advanced life support in a manikin model	✓		
5	Bonnin	1993	distinct criteria for termination of resuscitation in the out-of-hospital setting		✓	
6	Botran	2011	Chest compressions versus ventilation plus chest compressions: a randomized trial in a pediatric asphyxial cardiac arrest animal model	✓		
7	Brywczyński	2010	Emergency Medical Services Transport Decisions in Post traumatic Circulatory Arrest: Are National Practices Congruent?	✓		
8	Caralis	1992	Attitudes of medical-students, house staff, and faculty physicians toward euthanasia and termination of life-sustaining treatment	✓		
9	Cave	2009	Evaluation of the Association of Anaesthetists of Great Britain and Ireland lipid infusion protocol in bupivacaine induced cardiac arrest in rabbits	✓		
10	Chan	2013	Comparison of clinical prediction rules for termination of resuscitation of out-of-hospital cardiac arrests on arrival to emergency department		✓	
11	Charapov	2012	Cardiac arrest in the operating room requiring prolonged resuscitation	✓		
12	Considine	2009	Termination of resuscitation: Potential benefits of clinical prediction rules		✓	
13	Cooper	2007	Reliability testing and update of the Resuscitation Predictor Scoring (RPS) Scale		✓	
14	Darragh	2012	A low tilt waveform in the transthoracic defibrillation of ventricular arrhythmias during cardiac arrest	✓		
15	de Vos	1998	Decisions to terminate resuscitation		✓	
16	Deakin	2008	Changes in transthoracic impedance during sequential biphasic defibrillation	✓		
17	Diepenseifen	2011	Cardiopulmonary Resuscitation Ongoing CPR During Transport - When Does it Make Sense?		✓	
18	Elo	2005	Ethical considerations behind the limitation of cardiopulmonary resuscitation in Hungary - the	✓		



			role of education and training			
19	Goldberger	2012	Duration of resuscitation efforts and survival after in-hospital cardiac arrest: an observational study		✓	
20	Gonzalez-Mesa	2013	Unfavorable course in pregnancy-associated thrombotic thrombocytopenic purpura necessitating a perimortem Cesarean section: a case report.	✓		
21	Goto	2013	Termination-of-resuscitation rule for emergency department physicians treating out-of-hospital cardiac arrest patients: an observational cohort study			✓
22	Govindarajan	2012	Practice variability among the EMS systems participating in Cardiac Arrest Registry to Enhance Survival (CARES).	✓		
23	Hassan	1996	Prehospital cardiac arrest in Leicestershire: Targeting areas for improvement		✓	
24	Inomata	2011	[Usage of a defibrillator].	✓		
25	Jamerson	2008	Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients.	✓		
26	Kajino	2013	Current termination of resuscitation (TOR) guidelines predict neurologically favorable outcome in Japan.			✓
27	Kellermann	1993	Predicting the outcome of unsuccessful prehospital advanced cardiac life-support		✓	
28	Kingsnorth	2010	Family presence during trauma activations and medical resuscitations in a pediatric emergency department: an evidence-based practice project	✓		
29	Klein	2007	Another case of apparent death - A discussion of guidelines for emergency medical personnel in the pronouncement of death		✓	
30	Kolar	2008	Partial pressure of end-tidal carbon dioxide successful predicts cardiopulmonary resuscitation in the field: a prospective observational study		✓	
31	Koster	2008	Recurrent ventricular fibrillation during advanced life support care of patients with prehospital cardiac arrest	✓		
32	Lewis	2001	Monitoring a clinical trial conducted under the food and drug administration regulations allowing a waiver of prospective informed consent: The diaspirin cross-linked hemoglobin traumatic hemorrhagic shock efficacy trial	✓		
33	Lockey	2002	Recognition of death and termination of cardiac resuscitation attempts by UK ambulance personnel		✓	
34	Lockey	2001	Decision making by emergency physicians when assessing cardiac arrest patients on arrival at		✓	

			hospital			
35	Maertens	2013	Patients with cardiac arrest are ventilated two times faster than guidelines recommend: An observational prehospital study using tracheal pressure measurement	✓		
36	Martinez-Rubio	2003	Advances for treating in-hospital cardiac arrest: Safety and effectiveness of a new automatic external cardioverter-defibrillator	✓		
37	Memtsoudis	2006	The usefulness of transesophageal echocardiography during intraoperative cardiac arrest in noncardiac surgery	✓		
38	Millin	2013	Withholding and termination of resuscitation of adult cardiopulmonary arrest secondary to trauma: Resource document to the joint NAEMSP-ACSCOT position statements	✓		
39	Millin	2011	Termination of resuscitation of non-traumatic cardiopulmonary arrest: resource document for the National Association of EMS physicians position statement		✓	
40	Mohr	2003	To resuscitate or not? The emergency physician's decision in the prehospital setting		✓	
41	Morrison	2007	Inter-rater reliability and comfort in the application of a basic life support termination of resuscitation clinical prediction rule for out of hospital cardiac arrest	✓		
42	Morrison	2009	Validation of a universal prehospital termination of resuscitation clinical prediction rule for advanced and basic life support providers.			✓
43	Morrison	2007	Derivation and evaluation of a termination of resuscitation clinical prediction rule for advanced life support providers.			✓
44	Morrison	2006	Validation of a rule for termination of resuscitation in out-of-hospital cardiac arrest.			✓
45	Morrison	2008	Termination of resuscitation: a guide to interpreting the literature.	✓		
46	Morrison	2006	Summary of the methodology for the validation study for a termination of resuscitation clinical prediction rule.	✓		
47	NAEMSP	2003	Guidelines for withholding or termination of resuscitation in prehospital traumatic cardiopulmonary arrest	✓		
48	Niemann	2007	Is all ventricular fibrillation the same? A comparison of ischemically induced with electrically induced ventricular fibrillation in a porcine cardiac arrest and resuscitation model	✓		
49	Nurmi	2005	Layperson positioning of defibrillation electrodes guided by pictorial instructions	✓		
50	Omarcaigh	1993	Cessation of unsuccessful pediatric resuscitation - how long is too long	✓		
51	Ong	2007	Comparison of termination-of-resuscitation guidelines for out-of-hospital			✓

			cardiac arrest in Singapore EMS			
52	Ong	2006	Comparison of termination-of-resuscitation guidelines for basic life support: defibrillator providers in out-of-hospital cardiac arrest.			✓
53	Orlowski	1993	Forgoing life-supporting or death-prolonging therapy - a policy statement		✓	
54	Paal	2012	Termination of Cardiopulmonary Resuscitation in Mountain Rescue		✓	
55	Paulsen	2012	Empirical Hospital and Professional Charges for Patient Care Associated with Out of Hospital Cardiac Arrest Before and After Implementation of Therapeutic Hypothermia for Comatose Survivors	✓		
56	Pierce	1992	Metabolic demands and perceived exertion during cardiopulmonary-resuscitation	✓		
57	Reinhardt	2010	The Gottingen AED model	✓		
58	Richman	2008	Independent evaluation of an out-of-hospital termination of resuscitation (TOR) clinical decision rule.			✓
59	Ristagno	2012	Comparison of defibrillation efficacy between two pads placements in a pediatric porcine model of cardiac arrest	✓		
60	Roberts	2000	Adult and pediatric CPR: Attitudes and expectations of health professionals and laypersons	✓		
61	Rodriguez-Nunez	2006	Pediatric defibrillation after cardiac arrest: initial response and outcome	✓		
62	Roessler	2008	Guidelines for resuscitation 2005 - What is their effect, what is new?	✓		
63	Ruygrok	2009	Validation of 3 Termination of Resuscitation Criteria for Good Neurologic Survival After Out-of-Hospital Cardiac Arrest			✓
64	Sanders	2001	Searching for a predictive rule for terminating cardiopulmonary resuscitation.		✓	
65	Sasson	2009	A Qualitative Study to Identify Barriers to Local Implementation of Prehospital Termination of Resuscitation Protocols	✓		
66	Sasson	2008	Prehospital termination of resuscitation in cases of refractory out-of-hospital cardiac arrest.			✓
67	Schmidt	1995	Family response to out-of-hospital death	✓		
68	Schoenenberger	1994	Survival after failed out-of-hospital resuscitation - are further therapeutic efforts in the emergency department futile		✓	
69	Schultz	1996	Predicting in-hospital mortality during cardiopulmonary resuscitation		✓	
70	Sherbino	2010	Clinical decision rules for termination of resuscitation in out-of-hospital cardiac arrest.			Review of studies
71	Skrifvars	2010	Comparison of Helsinki and European Resuscitation Council "do not attempt to			✓

			resuscitate" guidelines, and a termination of resuscitation clinical prediction rule for out-of-hospital cardiac arrest patients found in asystole or pulseless electrical activity.			
72	Stockinger	2004	Additional evidence in support of withholding or terminating cardiopulmonary resuscitation for trauma patients in the field	✓		
73	Stratton	2008	Out-of-hospital unwitnessed cardiopulmonary collapse and no-bystander CPR: A practical addition to resuscitation termination guidelines		✓	
74	Strote	2008	Transfer of care is associated with longer unsuccessful resuscitations.		✓	
75	Taghavi	2012	Paramedics experiences and expectations concerning advance directives: A prospective, questionnaire-based, bi-centre study	✓		
76	Turner	2009	Timing of defibrillation shocks for resuscitation of rapid ventricular tachycardia: Does it make a difference?	✓		
77	Vaagenes	2003	Rapid rewarming after mild hypothermia accentuates the inflammatory response after acute volume controlled haemorrhage in spontaneously breathing rats	✓		
78	Valenti	1996	Impact of the implantable cardioverter-defibrillator on rehospitalizations	✓		
79	Verbeek	2002	Derivation of a termination-of-resuscitation guideline for emergency medical technicians using automated external defibrillators.	✓		
80	Wampler	2012	Cardiac arrest survival is rare without prehospital return of spontaneous circulation			
81	Wang	2013	Biphasic versus monophasic defibrillation in out-of-hospital cardiac arrest: a systematic review and meta-analysis	✓		
82	Wieneke	2009	Automatic External Defibrillator - Mode of Operation and Clinical Use	✓		
83	Willis	2006	Cardiopulmonary resuscitation after traumatic cardiac arrest is not always futile	✓		
84	Wirth	2009	Computed tomography during cardiopulmonary resuscitation using automated chest compression devices-an initial study	✓		
85	Wong	2007	The laryngeal mask airway prevents supraglottic leak during ventilation through an uncuffed cricothyroidotomy	✓		
86	Zive	2011	Variation in out-of-hospital cardiac arrest resuscitation and transport practices in the Resuscitation Outcomes Consortium: ROC Epistery-Cardiac Arrest	✓		

## Result of 'Snowballing'

Ser	First Author	Year	Title	Excluded by Title	Excluded by Abstract	Review
87	Bailey	2000	Termination of resuscitation in the prehospital setting for adult patients suffering nontraumatic cardiac arrest.		✓	
88	Goto	2013	Neurological outcomes in patients transported to hospital without a prehospital return of spontaneous circulation after cardiac arrest		✓	
90	Haukoos	2004	Prediction rules for estimating neurologic outcome following out-of-hospital cardiac arrest.		✓	

## Articles identified post-initial search

Ser	First Author	Year	Title	Excluded by Title	Excluded by Abstract	Review
92	Chiang	2015	Predictive performance of universal termination of resuscitation rules in an Asian community: are they accurate enough?			✓
89	Hauck	2015	Cardiac arrest with initial arrest rhythm of pulseless electrical activity: do rhythm characteristics correlate with outcome?		✓	
91	Iqbal	2015	Predictors of Survival and Favorable Functional Outcomes After an Out-of-Hospital Cardiac Arrest in Patients Systematically Brought to a Dedicated Heart Attack Center (from the Harefield Cardiac Arrest Study)		✓	
93	Cheong	2016	Termination of resuscitation rules to predict neurological outcomes in out-of-hospital cardiac arrest for an intermediate life support prehospital system			✓
94	Verhaerta	2016	Termination of resuscitation in the prehospital setting: A comparison of decisions in clinical practice vs. recommendations of a termination rule			✓

### **Appendix 3 - Summary of studies identified in literature review**

**Cheong, Li, Nausheen *et al*, (2016). Termination of Resuscitation Rules to Predict Neurological Outcomes in Out-of-Hospital Cardiac Arrest for an Intermediate Life Support Prehospital System** <sup>154</sup>

**Rule.** Two rules were validated:

1. A BLS-TOR rule, Termination where there is no ROSC, no defibrillation, and the arrest is not witnessed by EMS personnel.
2. An ALS-TOR rule, which recommends TOR when there is no ROSC, no defibrillation, the arrest is not witnessed by either bystanders or EMS personnel, and no bystander CPR is administered.

**EMS System.** A single-tier system run by the Singapore Civil Defense Force (SCDF), which operates at an intermediate life support (ILS) service, including AED, laryngeal mask airways (LMAs), administration of IV adrenaline and a limited range of other medications. Diagnosis of death at scene is only applicable for patients who are obviously dead (i.e., signs of rigor mortis, lividity, decapitation).

**Population.** The study used data from Singapore, which is a city-state with an area of 715 km<sup>2</sup> and a population of 5.31 million in 2012. Data included all OHCA patients over 18 years old and transported to 7 participating hospitals from April 2010 to May 2012. The mean age was 65.6. 68.7% were male

**Study design.** This was a retrospective cohort study based on data from a large, pre-existing database.

**Primary outcome(s).** The primary outcome measure was survival with good neurological outcome. The secondary outcome was survival to hospital discharge, or survival to 30 days of admission.

**Exclusion criteria.** Patients were excluded if: they were below the age of 18; were brought into the ED by means other than the EMS service; the OHCA was due to non-cardiac cause, as determined at scene (e.g., trauma, drowning, drug overdose, etc.); and patients who were obviously dead (e.g., rigor mortis, lividity, decapitation) or had DNACPR orders.

**Main results.** 2,193 eligible OHCA cases were reviewed. The BLS TOR guideline would have recommended TOR in 1,411 (64.3%) of all cases. Of these, none survived with good neurologic outcomes. For good neurologic outcome the specificity of BLS TOR rule was 100% (95% CI: 91.9% to 100%), and the PPV was 100% (95% CI: 99.7% to 100%). However, 5 (0.4%) survived to discharge (or 30 day in hospital survival). For survival the specificity of BLS TOR rule was 93.4% (95% CI: 85.3% to 97.8%), and the PPV was 99.7% (95% CI: 99.2% to 99.9%).

The ALS TOR rule would have recommended TOR in 587 (27.3%) cases. Of these none survived to hospital discharge with good neurologic outcome. The specificity of ALS TOR rule for predicting good neurologic outcome was 100% (95% CI: 91.9% to 100%), and the PPV was 100% (95% CI: 99.4% to 100%) for predicting survival with good neurologic outcome. One patient (0.2%) did survive, despite being recommended for TOR. The specificity of ALS TOR rule for predicting survival was 98.7% (95% CI: 92.9% to 99.8%), and the PPV was 99.8% (95% CI: 99.1% to 100%).

**Transport rate.** For the BLS rule – 35.6%. For ALS rule – 73.2%.

With this study both the ALS-TOR rule and the BLS-TOR rule meet Level 4 criteria for the hierarchy of evidence for CDRs.

**Chiang, Ko, Chang *et al*, (2015). Predictive performance of universal termination of resuscitation rules in an Asian community: are they accurate enough? <sup>155</sup>.**

**Rule.** Two rules were validated:

1. A BLS-TOR rule, Termination where there is no ROSC, no defibrillation, and the arrest is not witnessed by EMS personnel.
2. An ALS-TOR rule, which recommends TOR when there is no ROSC, no defibrillation, the arrest is not witnessed by either bystanders or EMS personnel, and no bystander CPR is administered.

The two rules were each assessed against three groups of EMS provider; BLS, ALS and mixed responders.

**EMS System.** This was a fire department-based BLS system with early defibrillation capability. From 2008 to 2010, a prehospital ALS service covered 3 of 12 administrative districts in Taipei, comprising a staff of 65 EMT paramedics. Although this system did not allow EMTs to pronounce death of OHCA patients in the field, the authors report anecdotal evidence that families may have chosen not to allow transport of the patient if they were very old or had been bedridden. Where patients had not been transported to the hospital, they were not included in the analyses.



**Population.** A metropolitan area of 272 km<sup>2</sup> with a registered population of 2.65 million and up to 3.0 million when daytime workers are also included. The majority of the population are Taiwanese and Chinese. Registered data of patients over 18 years suffering an OHCA from 1 January 2008 through 31 December 2009 were included. The mean age was 73.0. 62.7% were male.

**Study design.** This was a retrospective cohort study based on data from a large, pre-existing database.

**Primary outcome(s).** The primary outcome measure survival to hospital discharge.

**Exclusion criteria.** Patients were excluded if they had traumatic injuries or where resuscitation was not attempted due to obvious death or an existing DNACPR order.

**Main results.** 3489 eligible OHCA cases were reviewed. 1727 of these patients received only BLS care, 240 received ALS care and 1522 received mixed care. The BLS TOR guideline would have recommended TOR in 2,156 (61.8%) of all cases. Of these, 51 (2.4%) survived to hospital discharge. The specificity of BLS TOR rule was 74.1% (95% CI: 67.3% to 80.0%), and the PPV was 97.6% (95% CI: 96.9% to 98.29%). 240 eligible patients received ALS care. The ALS TOR rule would have recommended TOR in 82 (34.2%) cases. Of these 4 (4.9%) survived to hospital discharge. The specificity of ALS TOR rule was 81.8% (95% CI: 59.0% to 94.0%), and the PPV was 95.1 (95% CI: 87.3% to 98.4%) for predicting lack of survival. For all enrolled OHCA the ALS TOR guideline would have recommended 1,944 (55.7%) terminations. Of these, 48 (2.5%) survived. The specificity of ALS TOR guideline for all OHCA was 75.6% (95% CI: 68.9% to 81.3%), and the PPV was 97.5 (95% CI: 96.7% to 98.2%) for predicting lack of survival.

**Transport rate.** For the BLS rule against BLS response – 37.5%. For BLS against all OHCA – 61.7%. For the ALS rule against ALS response - 65.8%. For ALS against all OHCA – 44.2%.

With this study both the ALS-TOR rule and the BLS-TOR rule meet Level 4 criteria for the hierarchy of evidence for CDRs.

**Goto, Goto and Maeda (2013) Termination-of-resuscitation rule for emergency department physicians treating out-of-hospital cardiac arrest patients: an observational cohort** <sup>158</sup>

**Rule:** no prehospital ROSC, unshockable initial rhythm, and unwitnessed by bystanders.

**EMS System.** This was a fire department model with 804 fire departments, covering the whole of Japan, which has an area of approximately 378,000 km<sup>2</sup> and a population of approximately 127 million. Each ambulance has a crew of three emergency providers, which includes at least one emergency lifesaving technician. ALS measures in Japan are limited to advanced airway management and epinephrine. In this system all patients on whom resuscitation is attempted are transported to hospital.

**Population.** 105,030 adult OHCA victims who received EMS in Japan between January 2005 and 31 December 2009. Age was 76 (64 to 84), and 58.7% were male.

**Study design.** This was a retrospective cohort study based on data from a large, pre-existing database.

**Primary outcome(s).** The primary outcome measure was overall rates of one-month survival and CPC categories 1 and 2.

**Exclusion criteria.** Patients were excluded if they were under 18 years; if there was missing 1-month CPC data; where a physician-manned ambulance attended; where call-to-response time unknown; where AED use unknown; or where the data was improper

**Main results.** TOR rule showed a specificity of 0.903 (95% CI, 0.894 to 0.911), sensitivity of 0.595 (95% CI, 0.592 to 0.598) PPV of 0.993 (95% CI, 0.992 to 0.993) and NPV of 0.078 (95% CI, 0.077 to 0.079).

**Transport rate.** The transport rate was 42.7%

With this study the rule meet Level 4 criteria for the hierarchy of evidence for CDRs.

**Kajino, Kitamura, Iwami *et al*, (2013). Current termination of resuscitation (TOR) guidelines predict neurologically favourable outcome in Japan <sup>153</sup>.**

**Rule.** Two rules were validated:

1 A BLS-TOR rule, Termination where there is no ROSC, no defibrillation, and the arrest is not witnessed by EMS personnel.

2. An ALS-TOR rule, which recommends TOR when there is no ROSC, no defibrillation, the arrest is not witnessed by either bystanders or EMS personnel, and no bystander CPR is administered.

**EMS System.** This was a fire department model with 804 fire departments, covering the whole of Japan, which has an area of approximately 378,000 km<sup>2</sup> and a

population of approximately 127 million. Each ambulance has a crew of three emergency providers, which includes at least one emergency lifesaving technician. ALS measures in Japan are limited to advanced airway management and epinephrine. In this system all patients on whom resuscitation is attempted are transported to hospital.

**Population.** Patients aged  $\geq 18$  years who had an OHCA of presumed cardiac origin, treated by EMS, and were transported to hospital from January 1, 2005 to December 31, 2009. Patients were classified according to the level of EMS care they received. Those who received only BLS were classified into the BLS group. Those who received BLS plus ALS were classified into the ALS group. Out of 530,084 patients with resuscitation attempts, 294,193 were enrolled. The mean age was 75.5 years, 56.8% were male.

**Study design.** This was a retrospective cohort study based on data from a large, pre-existing database.

**Primary outcome(s).** The primary outcome measure was neurologically favourable one-month survival.

**Exclusion criteria.** Patients were excluded if they were deemed to have obvious signs of death, such as decapitation, incineration, decomposition, rigor mortis, or dependent lividity.

**Main results.** 151,152 eligible patients received only BLS care. The BLS TOR guideline would have recommended TOR in 113,140 (74.9%) cases. Of these, 193 (0.2%) had one-month survival with neurologically favourable outcome. The specificity of BLS TOR rule was 96.8% (95% CI: 96.3% to 97.2%), and the PPV was

99.8% (95% CI: 99.8% to 99.9%) for predicting no neurologically favourable one-month survival. For one-month survival, the specificity of BLS TOR rule was 87.8% (95% CI: 87.2% to 88.4%), and the PPV was 99.0% (95% CI: 98.9% to 99.0%).

137,986 eligible patients received ALS care. The ALS TOR rule would have recommended TOR in 41,030 (27.1%) cases. Of these 37 (0.1%) survived to hospital discharge with neurologically favourable outcomes. The specificity of ALS TOR rule was 98.1% (95% CI: 97.3% to 98.6%), and the PPV was 99.9 (95% CI: 99.8% to 99.9%) for predicting lack of one-month survival with neurologically favourable outcome. The specificity of ALS TOR rule, for one-month survival was 92.3% (95% CI: 91.6% to 93.0%), and the PPV was 99.0% (95% CI: 98.9% to 99.1%).

**Transport rate.** For the BLS rule – 45.6%. For the ALS rule - 69.0%.

With this study both the ALS-TOR rule and the BLS-TOR rule meet Level 4 criteria for the hierarchy of evidence for CDRs.

**Morrison, Kiss, Verbeek *et al* (2006) Validation of a rule for termination of resuscitation in out-of-hospital cardiac arrest. New England Journal of Medicine <sup>147</sup>.**

**Rule.** Termination where there is no ROSC, no defibrillation, and the arrest is not witnessed by EMS personnel.

**EMS System.** 12 participating sites in one of 24 EMS systems in Ontario, Canada (communities with populations of 40,000 to 2.5 million persons). This system included only Emergency Medical Technicians (EMTs) trained in the use of an

automated external defibrillator (AED), who were not previously using any other TOR CDRs, but were transporting all patients to hospital.

**Study Population.** Consecutively enrolled adult patients who were treated for OHCA of presumed cardiac aetiology between January 1, 2002, and January 30, 2004. Of 1620 OHCA, 1240 patients were enrolled. The mean age was 69.2 years, 69.0% were male.

**Study design.** This was a prospective, observational validation study. After a patient was transferred to the receiving hospital, the EMTs completed a data-collection form. This included relevant clinical characteristics of the cardiac arrest and all elements of the prediction rule. Patients were categorised for termination or transport according to the recommendations of the prediction rule.

**Primary outcome(s).** The outcomes were analysed as either “died” or “survived”. A secondary outcome(s) of cerebral performance, either at discharge from the hospital or at six months for those in the hospital at that point was also analysed.

**Exclusion criteria.** Patients were excluded if they received ALS interventions (e.g., intubation or the administration of intravenous fluids and medication); those who had a written or oral do-not-resuscitate order; those who had an arrest attributable to an obvious non-cardiac aetiology (e.g., trauma or asphyxia); and those under 16 years of age.

**Main results.** Of the 776 patients for whom the prediction rule recommended the termination of basic life support resuscitation efforts, 4 survived (0.5 %; 95 % CI: 0.1% to 0.9 %). Of these, 3 were considered to have good cerebral performance. The CDR had a positive predictive value for death of 99.5% (95 % CI: 98.9 to 99.8

%), a specificity of 90.2% (95 % CI: 88.4% to 91.8%), and sensitivity of 64.4% (95% CI: 61.6% to 67.0%)

**Transport rate.** 35.6%

With this study the BLS-TOR rule meets the Level 2 criteria for the hierarchy of evidence for CDRs

**Morrison, Verbeek, Vermeulen *et al*, (2007). Derivation and evaluation of a termination of resuscitation clinical prediction rule for advanced life support providers <sup>112</sup>.**

**Rule.** Two rules were validated:

1. A BLS-TOR rule which recommends TOR where there is no ROSC, no defibrillation, and the arrest is not witnessed by EMS personnel.
2. An ALS-TOR rule which recommends TOR when there is no ROSC, no defibrillation, the arrest is not witnessed by either bystanders or EMS personnel, and no bystander CPR is administered.

**EMS System.** Paramedic EMS crews located in 21 urban and rural communities. It is unclear whether a TOR CDR was available to the providers during the study period, but all patients undergoing resuscitation attempts were included for the purposes of this validation.

**Population.** Of 5274 cardiac arrest patients attended to by paramedics, 4673 were included in the study. The mean age was 66 years. 374 (62%) were male.

**Study design.** This was a retrospective cohort study based on data from a large, pre-existing database.

**Primary outcome(s).** The primary outcome was defined as survival to hospital discharge.

**Exclusion criteria.** Patients were excluded from the study if the arrest was of a non-cardiac aetiology, including trauma; the patient was obviously dead (rigor mortis, lividity, decomposition or decapitation); the patient was under 16 years old; ALS was available at the scene before the arrival of EMS; a DNACPR order was present; or the event was determined not to be OHCA after review by the steering committee.

**Main results.** The BLS TOR guideline would have recommended TOR in 2263 patients (48%). Of these, none (0%) survived to hospital discharge. The PPV for death was 99.8% (95% CI: 99.6% to 99.9%). Sensitivity (the ability to identify survivors) was 100% (95% CI: 99.9% to 100%), specificity (the ability to identify patients who died) was 50% (95% CI: 49% to 52%) and the negative predictive value (probability that a patient who fulfilled the TOR rule would not survive), was 100% (95% CI: 99.9% to 100%).

The ALS TOR guideline would have recommended TOR in 1425 cases (30%). Of these none survived to hospital discharge. The sensitivity was 100% (95% CI: 99.9% to 100%). The specificity was 32% (95% CI: 30% to 33%). The negative predictive value was 100% (95% CI: 99.9% to 100%).

**Transport rate.** For the BLS rule – 51.6%. For the ALS rule – 69.9%.

With this study both the ALS-TOR rule and the BLS-TOR rule meet Level 4 criteria for the hierarchy of evidence for CDRs.



**Morrison, Verbeek, Zhan *et al*, (2009). Validation of a universal prehospital termination of resuscitation clinical prediction rule for advanced and basic life support providers <sup>151</sup>.**

**Rule.** Two rules were validated:

1. A BLS-TOR rule, Termination where there is no ROSC, no defibrillation, and the arrest is not witnessed by EMS personnel.
2. An ALS-TOR rule, which recommends TOR when there is no ROSC, no defibrillation, the arrest is not witnessed by either bystanders or EMS personnel, and no bystander CPR is administered.

**EMS System.** This system used a tiered response involving Police, Fire, defibrillation-only EMTs, and Paramedic crews from EMS Systems in the city of Toronto and 5 adjacent municipalities (Peel, Durham, Hamilton, Muskoka and Simcoe), plus a province-wide air ambulance service. The EMS systems served a population of 6.7 million by land and 11 million by air. There is evidence that Paramedic crews within this study were using existing TOR CDRs, as it is reported that 1069 patients (44.3%) died on scene. It is unclear what tool was used to terminate these attempts, but appear to be based on decisions made by physicians providing medical control to ambulance staff.

**Population.** The registry included 4854 cases of OHCA between from 1 April 2006 to 1 April 2007. Of 4854 patients, 2415 patients were enrolled. The mean age was 69.4 years, 63% were male

**Study design.** This was a retrospective cohort study of data prospectively collected from 1 April 2006 to 1 April 2007 by one site.

**Primary outcome(s).** The primary outcome measure was to determine if any patient survived to hospital discharge having met either the BLS or ALS TOR criteria.

**Exclusion criteria.** Patients were excluded from the study if the OHCA was of non-cardiac aetiology, including trauma; were obviously dead as defined by local legislation; were under the age of 18; had a valid 'Do Not Resuscitate' order.

**Main results.** The BLS TOR guideline would have recommended TOR in 1302 patients (54.3%). Of these, none (0%) survived to hospital discharge. The PPV for death was 100% (95% CI: 99.8% to 100%). The specificity was 100% (95% CI: 99.8% to 100%). The sensitivity was 57.5% (95% CI: 57.3% to 57.7%).

The ALS TOR guideline would have recommended TOR in 743 cases (31%). Of these none survived to hospital discharge. The PPV for death was 100.0% (95% CI: 99.7% to 100.0%). The specificity was 100% (95% CI: 99.8% to 100%). The sensitivity was 32.8% (95% CI: 30.8% to 34.7%).

**Transport rate.** For the BLS rule – 45.6%. For the ALS rule - 69.0%.

With this study both the ALS-TOR rule and the BLS-TOR rule meet Level 4 criteria for the hierarchy of evidence for CDRs.

**Ong, Jaffey, Stiell *et al* (2006). Comparison of termination-of-resuscitation guidelines for basic life support: Defibrillator providers in out-of-hospital cardiac arrest<sup>110</sup>.**

**Rule.** Three rules were validated:

1. (Petrie <sup>222</sup>) TOR where the initial rhythm is asystole and response time is greater than 8 minutes.
2. (Verbeek *et al* <sup>111</sup>) TOR where there is no ROSC, no defibrillation, and the arrest is not witnessed by EMS personnel.
3. The final rule (Marsden, Ng, Dalziel *et al* <sup>223</sup>) will not be discussed. This rule proposes termination if there is no initial shockable rhythm; no evidence of CPR in the past fifteen minutes; no evidence of drowning, hypothermia, poisoning or overdose, and the patient is neither under eighteen years nor pregnant; there is no ROSC after one minute of CPR; there is asystole for ten seconds. As current UK guidelines allow for diagnosis of death (i.e. the decision can be made not to start a resuscitation attempt) when no CPR has been performed for the past fifteen minutes and the patient is in an asystolic rhythm, this subset of patients will not have resuscitation attempted by UK ambulance staff, and so do not require a TOR decision to be made.

**EMS System.** Data collected from 21 Ontario urban or suburban communities, which range in population from 16,000 to 750,000 (total 2.7 million). The EMS system is two-tier, with AED–equipped fire fighters, followed by BLS defibrillator ambulance providers. No TOR CDR was available to the providers, and all patients undergoing resuscitation attempts were transported.

**Population.** Of 21,913 OHCA patients taken from the registry between 1988 and 2003, 13,684 were enrolled in the study. The mean age was 69.1 years. 67.3% were male.

**Study design.** This was a retrospective cohort study based on data from a, pre-existing database.

**Primary outcome(s).** The primary outcome was survival to hospital discharge.

**Exclusion criteria.** Patients were excluded from the study if they were younger than 16 years, showed sign of decomposition, rigor mortis, or were clearly non–cardiac aetiology (eg, trauma, drowning, choking).

**Main results.** The Petrie guideline would have recommended TOR in 1,293 cases. Of these, 1 (0.08%) survived. The Verbeek guideline would have recommended TOR in 6,908 cases. Of these, 3 (0.04%) survived. The comparative sensitivity (ability to predict survivors) was 99.8% (95% CI: 99.5% to 100.0%) (Petrie rules), and 99.5% (95% CI: 99.0% to 100.0%) (Verbeek rules). Negative predictive value (ability of TOR guideline to predict death) was 99.9% (95% CI: 99.8% to 100.0%) (Petrie rules), and 100.0% (95% CI: 99.9% to 100.0%) (Verbeek rules).

**Transport rate.** For the Petrie rule – 90.6%. For the Verbeek rule – 49.5%.

With this study both the Petrie and the Verbeek rules meet Level 4 criteria for the hierarchy of evidence for CDRs.

**Ong, Tan, Ng *et al*, (2007). Comparison of termination-of-resuscitation guidelines for out-of-hospital cardiac arrest in Singapore EMS <sup>149</sup>.**

**Rule.** Three rules were validated:

1. (Petrie <sup>222</sup>) TOR where the initial rhythm is asystole and response time is greater than 8 minutes.

2. (Verbeek et al <sup>111</sup>)TOR where there is no ROSC, no defibrillation, and the arrest is not witnessed by EMS personnel.

3. The final rule (Marsden, Ng, Dalziel et al <sup>223</sup>) will not be discussed, as the patient group would be captured by TOR guidelines currently in place for all UK ambulance services.

**EMS System.** Data collected from Singapore, which has a population of 4.1 million. The EMS system is run by the Singapore Civil Defence Force and utilises BLS providers with AEDs. No TOR CDR was available to the providers, and all patients undergoing resuscitation attempts were transported.

**Population.** Between 1 October 2001 and 14 October 2004, 2269 were enrolled in the study. The mean age was 61.1 years. 68.4% were male.

**Study design.** This was a retrospective cohort study based on data from a, pre-existing database.

**Primary outcome(s).** The primary outcome was defined as the patient leaving the hospital alive or survival to 30 days post cardiac arrest.

**Exclusion criteria.** Patients were excluded from the study if they were 'obviously dead' as defined by the presence of decomposition, rigor mortis or dependant lividity.

**Main results.** The Petrie guideline would have recommended TOR in 716 cases. Of these, 2 (0.28%) survived. The Verbeek guideline would have recommended TOR in 1559 cases. Of these, 6 (0.38%) survived. The comparative sensitivity (ability to predict survivors) was 93.8% (95%CI: 79.9% to 98.3%) (Petrie) and 81.3% (95%CI: 64.7% to 91.1%) (Verbeek). Negative predictive value (ability of TOR guideline to

predict death) was 99.7% (95%CI: 99.0% to 100.0%) (Petrie) and 99.6% (95%CI: 99.2% to 99.8%) (Verbeek).

**Transport rate.** For the Petrie rule – 68.4% For the Verbeek rule –31.3%.

With this study both the Petrie and the Verbeek rules meet Level 4 criteria for CDRs .

**Richman, Vadeboncoeur, Chikani *et al* (2008). Independent evaluation of an out-of-hospital termination of resuscitation (TOR) clinical decision rule <sup>148</sup>.**

**Rule.** Termination where there is no ROSC, no defibrillation, and the arrest is not witnessed by EMS personnel.

**EMS System.** 30 EMS systems in Arizona (population 5,939,292). These included a mix of EMT-Basics, EMT-Intermediates and EMT-Paramedics. Existing rules allowed for crews not to initiate resuscitation if the patient was over 18 years of age and there were obvious sign of death, such as rigor mortis. Otherwise, all resuscitation attempts were transported.

**Population.** Consecutively enrolled adults in non-traumatic OHCA between October 2004 and October 2006. Of 2,239 eligible OHCA, 2,180 patients were enrolled. The mean age was 64 years, 65% were male.

**Study design.** This was a retrospective cohort analysis, using data taken from ambulance first care reports. Patients were categorised for termination or transport according to the recommendations of the prediction rule.

**Primary outcome(s).** The primary outcome was survival to hospital discharge.

**Exclusion criteria.** Patients were excluded if they had obvious signs of death (e.g. lividity, rigor, decapitation).

**Main results.** It was reported that of 1,160 (53%) of patients who met all three TOR criteria, only one (0.09%; 95%CI: 0 to 0.5%) survived to hospital discharge. However, only 804 patients for whom the BLS TOR rule recommended TOR were transported to hospital. The potential outcomes for those not transported cannot be assessed, as they did not get the benefit of full hospital resuscitation. When this group is excluded from the calculation, survival to hospital discharge of those recommended for TOR increases to 0.12%.

**Transport rate.** 46.8%.

With this study the BLS-TOR rule meet Level 4 criteria for CDRs

**Ruygrok, Byyny, Haukoos *et al*, (2009). Validation of 3 Termination of Resuscitation Criteria for Good Neurologic Survival After Out-of-Hospital Cardiac Arrest** <sup>168</sup>

**Rule.** Three rules were validated:

1. A BLS-TOR rule, Termination where there is no ROSC, no defibrillation, and the arrest is not witnessed by EMS personnel.
2. An ALS-TOR rule, which recommends TOR when there is no ROSC, no defibrillation, the arrest is not witnessed by either bystanders or EMS personnel, and no bystander CPR has been administered.

3. A neurologic TOR rule, which recommends TOR when the OHCA is not witnessed by a bystander or EMS personnel; patient aged 78 years or older; or asystole as the initial arrest rhythm.

**EMS System.** This was a 2-tiered response system, with fire-based first responders providing BLS, including use of AEDs, and ALS paramedic responders. It is unclear whether there was an existing TOR CDR in place during this study. However, all resuscitations attempted by Paramedics were included for statistical purposes.

**Population.** A secondary analysis of the Denver Cardiac Arrest Registry, which includes consecutive adult patients (age  $\geq 18$  years) who had non-traumatic OHCA from January 1, 2003 to December 31, 2004. Of the 715 patients included in this study, the median age was 65 years, and 69% were male.

**Study design.** This was a secondary analysis study based on data from a pre-existing database.

**Primary outcome(s).** The primary outcome measure for this study was survival to hospital discharge with good neurologic function as defined by a Cerebral Performance Categories Scale score of 1 or 2.

**Exclusion criteria.** Patients were excluded if they experienced trauma resulting in arrest or were younger than 18 years.

**Main results.** 715 (36%) of recorded patients were enrolled on the study. The BLS TOR guideline would have recommended TOR in 231 (32%) cases. The ALS TOR rule would have recommended TOR in 162 (23%) cases. The neurologic TOR rule would have recommended TOR in 39 (5%) cases. The proportion of patients with



good neurological survival to hospital discharge correctly identified for continued resuscitation was 100% (95% CI: 92% to 100%) for all 3 TOR criteria.

**Transport rate.** For the BLS rule – 70.2%. For the ALS rule – 77.3%. For the neurologic TOR 94.5%.

With this study both the ALS-TOR rule, the BLS-TOR rule and the neurologic TOR rule meet Level 4 criteria for CDRs.

**Sasson, McNally, Krass *et al*, (2008). Prehospital termination of resuscitation in cases of refractory out-of-hospital cardiac arrest <sup>150</sup>.**

**Rule.** Two rules were validated:

1. A BLS-TOR rule, Termination where there is no ROSC, no defibrillation, and the arrest is not witnessed by EMS personnel.
2. An ALS-TOR rule, which recommends TOR when there is no ROSC, no defibrillation, the arrest is not witnessed by either bystanders or EMS personnel, and no bystander CPR is administered.

**EMS System.** 19 EMS agencies and 111 hospitals located in 8 US cities: Anchorage, Alaska; metropolitan Atlanta, Georgia; Boston, Massachusetts; Raleigh, North Carolina; Cincinnati, Ohio; Columbus, Ohio; Austin, Texas; and Houston, Texas. Local TOR CDRs were in place at the time of the study. This is evidenced by 947 (17.2%) patients being pronounced dead on scene. No details of these existing CDRs are reported.

**Population.** The registry included 7235 cases of OHCA between October 2004 and October 2006. Of 7235 patients, 5505 patients were enrolled. The mean age was 64.4 years, 60% were male

**Study design.** This was a retrospective cohort study based on data from a large, pre-existing registry.

**Primary outcome(s).** The main outcome measures were the specificity and positive predictive value of both the BLS and ALS rules for identifying patients with OHCA who likely would not survive to hospital discharge.

**Exclusion criteria.** Patients were excluded from the register if EMS personnel determined that arrest was due to a non-cardiac aetiology (e.g. trauma, electrocution, drowning, or respiratory); Resuscitation was not attempted based on local protocols (e.g. obvious signs of death such as rigor mortis, decomposition, lividity); or the patient was younger than 16 years.

**Main results.** The BLS TOR guideline would have recommended TOR in 2592 patients (47.1%). Of these, 5 (0.2%) survived to hospital discharge. Of these, four were documented as having good cerebral performance. The PPV for death was 99.8% (95% CI: 99.6% to 99.9%).

The ALS TOR guideline would have recommended TOR in 1192 cases (21.7%). Of these none survived to hospital discharge. The PPV for death was 100.0% (95% CI: 99.7% to 100.0%).

**Transport rate.** For the BLS rule – 52.9%. For the ALS rule – 78.3%.

With this study both the ALS-TOR rule and the BLS-TOR rule meet Level 4 criteria for the hierarchy of evidence for CDRs.

**Skrifvars, Vayrynen, Kuisma *et al*, (2010). Comparison of Helsinki and European Resuscitation Council “do not attempt to resuscitate” guidelines, and a termination of resuscitation clinical prediction rule for out-of-hospital cardiac arrest patients found in asystole or pulseless electrical activity <sup>167</sup>.**

**Rule.** Three rules were validated:

1. Current guidelines of the European Resuscitation Council (not reported here, as it is the equivalent of that currently used by the Trust, as detailed previously).

2. Helsinki “do not attempt to resuscitate” guidelines:

- a) In asystolic arrests: Termination where there is a delay in arrival of the ambulance exceeding 15min, or if ROSC cannot be achieved despite 20min of ALS.
- b) In witnessed PEA: Termination where there is a delay in arrival of the ambulance exceeding 15min, or if ROSC is not achieved within 20min of ALS.
- c) In un-witnessed PEA: Termination where ROSC is not achieved within 10min of ALS.

3. An ALS-TOR rule, which recommends TOR when there is no ROSC, no defibrillation, the arrest is not witnessed by either bystanders or EMS personnel, and no bystander CPR is administered, but which was applied here only to patients presenting in a non-shockable rhythm.

**EMS System.** Nurses or paramedics and Emergency Medical Technicians throughout Sweden. In this system, resuscitation attempts can be terminated in cases of ongoing asystole despite 30min of CPR.

**Population.** Of 44121 OHCA patients on the Swedish Cardiac Arrest registry taken from 1990 to December 2007, 12107 with asystole or PEA as the initial rhythm were enrolled in the study. Patients with an arrest of non-cardiac cause were also included (excluding patients with drowning or trauma). The mean age was 71 years. 66% were male.

**Study design.** This was a retrospective cohort study based on data from a large, pre-existing database.

**Primary outcome(s).** The primary outcome was defined as survival at one month from the arrest.

**Exclusion criteria.** Patients were excluded from the study if it was an EMS-witnessed arrest; patients with a shockable initial rhythm; patients in whom the initial rhythm was not specified as either asystole or PEA; patients with drowning or trauma as the cause of the arrest.

**Main results.** The Helsinki guidelines guideline would have recommended TOR in 11315 patients (54.6%). Of these, 57 (0.5%) survived to hospital discharge: sensitivity: 53.3% (95% CI: 52.4% to 54.2%), specificity: 81.9% (95% CI: 73.7% to 88.4%), PPV: 99.7% (95% CI: 99.5% to 99.8%), NPV: 1.7% (95% CI: 1.4% to 2.0%).

The ALS rule would have recommended TOR in 5466 patients (26.4%). Of these, 2 (0.04%) survived. sensitivity: 23.4% (95% CI: 23.1% to 24.6%), specificity: 99.2%

(95% CI: 95.3% to 99.9%), PPV: 99.9% (95% CI: 99.8% to 100.0%), NPV: 1.2% (95% CI: 1.0% to 1.5%)

**Transport rate.** For the Helsinki rule – 45.3%. For the ALS rule – 73.6%.

With this study both the Helsinki and the ALS-TOR rules meet Level 4 criteria for the hierarchy of evidence for CDRs.

**Verhaerta, Bonnesa, Nas *et al* (2016) Termination of resuscitation in the prehospital setting: A comparison of decisions in clinical practice vs. recommendations of a termination rule <sup>157</sup>.**

**Rule** This study compared the ALS-TOR rule, which recommends TOR when there is no ROSC; no defibrillation; the arrest is not witnessed by either bystanders or EMS personnel; and no bystander CPR is administered, with current termination results. The study did not provide details of the reasons for current terminations, so these will not be discussed further.

**EMS System.** An ALS Paramedic response of two vehicles is sent to each suspected cardiac arrest, with additional police and fire service BLS-AED personnel if required.

**Population.** The study used data from Gelderland-Zuid in Holland, which has a population of 530,000 and covers 1040 km<sup>2</sup>, including urban, suburban and rural areas. Data included all OHCA patients over 18 years old from April 2008 to January 2011. The mean age was 66 years and 69% was male.

**Study design.** This was a retrospective cohort study.

**Primary outcome(s).** The primary outcome measure was in-field termination of resuscitation

**Exclusion criteria.** Patients were excluded if: they were below the age of 18; traumatic arrests (including hanging and drowning); and patients with DNACPR orders

**Main results.** A total of 598 patients were studied. 17% survived to hospital discharge. The ALS guideline would have recommended termination for 35 (6%) patients. None of these survived to discharge. The sensitivity of the rule was 7% (35/477) and specificity 100% (89/89). The NPV and PPV of the ALS-TOR rule were: 17% (89/531) and 100% (35/35), respectively.

**Transport rate.** For ALS rule – 94%.

With this study the ALS-TOR rule meets Level 4 criteria for the hierarchy of evidence for CDRs.

## APPENDIX 4 – R&D approval



North West Ambulance Service **NHS**  
NHS Trust

Headquarters  
Ladybridge Hall  
399 Chorley New Road  
Heaton, Bolton  
BL1 5DD  
Tel: 01204 498400  
Fax: 01204 498422  
www.nwas.nhs.uk

Matthew House

11<sup>th</sup> October 2013

Dear Matthew,

Re: Pre-Hospital Termination of Resuscitation

Thank you for approaching Nwas NHS Trust with regard to your study, and for completing the Trust R&D Proposal pro-forma.

I am pleased to advise you following review by the Senior Medical Directorate Team (SMT) a decision has been made to formally approve and adopt your phase 1 of your study into the Nwas current R&D portfolio. In order to progress with approval of phase 2 of your study we will need to see NHS Research Ethics Committee approval. However you can consider this letter as approval in principle for the overall study.

Please ensure that you have made yourself familiar with the Nwas R&D Framework requirements; the framework can be located on Nwas intranet or I can forward a copy on to you should you require.

Your project has been assigned the following unique number and this should be indicated on all correspondence with regard to your study: **Nwas 2013\_2014 024**

The next step is for you to provide update reports, so that the SMT and other sub-committees can be informed of your projects progress.

I take this opportunity to wish you well with your study, and do not hesitate to contact me should you require any further assistance with the Nwas R&D Framework process.

Kind Regards,

pp *M. Kane*

Maria Kane  
Clinical Quality Project Manager

Mary Peters  
Senior Clinical Quality Manager

Headquarters: Ladybridge Hall, 399 Chorley New Road, Bolton, BL1 5DD

Chairman: Mrs M Whymam MBE

Chief Executive: Mr D Humel



Delivering the right care, at the right time, in the right place

11 February 2014

Mr Matthew House  
Advanced Paramedic  
North West Ambulance NHS Trust  
17 Ruskin Close  
High Harrington  
Workington  
CA14 4LP

Dear Mr House

**Study title:** Pre-Hospital Termination of Resuscitation  
**REC reference:** 14/YH/0035  
**IRAS project ID:** 142981

Thank you for your email of 05 February 2014, responding to the Proportionate Review Sub-Committee's request for changes to the documentation for the above study.

The revised documentation has been reviewed and approved by the sub-committee.

We plan to publish your research summary wording for the above study on the NRES website, together with your contact details, unless you expressly withhold permission to do so. Publication will be no earlier than three months from the date of this favourable opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to withhold permission to publish, please contact the REC Manager Miss Sarah Grimshaw, [nrescommittee.yorkandhumber-leedseast@nhs.net](mailto:nrescommittee.yorkandhumber-leedseast@nhs.net).

#### **Confirmation of ethical opinion**

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised.

#### **Ethical review of research sites**

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

#### **Conditions of the favourable opinion**

The favourable opinion is subject to the following conditions being met prior to the start of the study.



Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at <http://www.rdforum.nhs.uk>.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations.

#### Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publicly accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to contest the need for registration they should contact Catherine Blewett ([catherineblewett@nhs.net](mailto:catherineblewett@nhs.net)), the HRA does not, however, expect exceptions to be made. Guidance on where to register is provided within IRAS.

**It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).**

#### Approved documents

The documents reviewed and approved by the Committee are:

Document	Version	Date
Investigator CV	Mathew House CV	22 January 2014
Other: Joanne Gray CV		
Other: Letter from Mary Peters re approval of study		11 October 2013
Participant Information Sheet	1.1	05 February 2014
Protocol	1.0	22 January 2014
REC application	3.5	22 January 2014
Response to Request for Further Information	Matthew House	05 February 2014

#### Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

A Research Ethics Committee established by the Health Research Authority

## After ethical review

### Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

### Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

Further information is available at National Research Ethics Service website > After Review

14/YH/0035	Please quote this number on all correspondence
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We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at <http://www.hra.nhs.uk/hra-training/>

With the Committee's best wishes for the success of this project.

Yours sincerely



pp  
Dr Carol Chu  
Chair

Email: [nrescommittee.yorkandhumber-leedseast@nhs.net](mailto:nrescommittee.yorkandhumber-leedseast@nhs.net)

Enclosures: "After ethical review – guidance for researchers" SL-AR2

Copy to: Mary Peters, North West Ambulance Service NHS Trust



*Professor Kathleen McCourt, CBE FRCN  
Executive Dean*

*This matter is being dealt with by:*

*Professor Olivier Sparagano  
Associate Dean  
Faculty of Health & Life Sciences  
Northumberland Building  
Newcastle upon Tyne  
NE1 8ST*

18 June 2014

Dear Matthew

**Faculty of Health and Life Sciences Research Ethics Review Panel  
Title: Pre-Hospital Termination of Resuscitation**

Following resubmission of the above proposal, I am pleased to inform you that University approval has been granted on the basis of this resubmitted proposal and subject to compliance with the University policies on ethics and consent and any other policies applicable to your individual research. You should also have recent Disclosure & Barring Service (DBS) and occupational health clearance if your research involves working with children and/or vulnerable adults.

We note that full sponsorship and indemnity of your study is provided by North West Ambulance Service NHS Trust.

The University's Policies and Procedures are available from the following web link:  
<https://www.northumbria.ac.uk/static/5007/research/reghandbook.pdf>

All researchers must also notify this office of the following:

- Commencement of the study;
- Actual completion date of the study;
- Any significant changes to the study design;
- Any incidents which have an adverse effect on participants, researchers or study outcomes;
- Any suspension or abandonment of the study;
- All funding, awards and grants pertaining to this study, whether commercial or non-commercial;
- All publications and/or conference presentations of the findings of the study.

We wish you well in your research endeavours.

Yours sincerely

Jim Clark  
Chair, Faculty Research Ethics Review Panel

## APPENDIX 5 - Participant information



North West Ambulance Service **NHS**  
NHS Trust

### Pre-Hospital Termination of Resuscitation Study Information Sheet

These forms are part of a study that is looking at the patients we attempt to resuscitate and their outcomes. We are trying to establish whether there are any factors, over and above present Termination of Resuscitation (ToR) Guidelines, which can be used to determine that resuscitation efforts will not be successful.

The forms will not be used to audit how you have performed the resuscitation; rather, the information from these forms will be compared against the actual survival outcomes of the patients.

Please complete one of these forms after **ALL** cardiac arrests where resuscitation is attempted or continued by NWS crews. Please complete the forms as fully as you can, so that we can capture all the relevant information.

These forms **MUST NOT** be used to determine whether or not to transport a patient to hospital following a cardiac arrest.

**At all times, follow NWS ToR Guidelines or the advice of an Advanced Paramedic in determining whether to transport your patient.**

Once completed, the forms should be left on station, in the designated area, from where they will be collected and sent via internal mail to Matt House at Salkeld Hall, Cumbria, for analysis.

Please note that by completing these forms, you consent to the information on them being used for the purposes of this study.

**We thank you for your time in completing this documentation**

For further information, please contact Matt House:

Email [matthew.house@nwas.nhs.uk](mailto:matthew.house@nwas.nhs.uk)

Tel: 07812 305548

## APPENDIX 6 - TOR Form

# Termination of Resuscitation Study

Complete this form after **ALL** cardiac arrests where resuscitation is attempted or continued by NWAS crews **and the patient is transported to hospital**.

**This should NOT be used to determine whether or not to transport a patient to hospital following a cardiac arrest.**

At all times, follow NWAS ToR Guidelines or the advice of the Clinical Support Hub or an Advanced Paramedic in determining whether to transport.

INCIDENT NUMBER \_\_\_\_\_

DATE \_\_\_\_\_

TABLE B	YES	NO
Presumed cardiac cause		



If **NO** – Stop here  
If **YES** – Complete Table C



TABLE C	YES	NO
Patient is thought to be pregnant		
Patient is under eighteen years old		
Was the presenting (first) rhythm shockable (VF/VT)		
Was ROSC achieved before transport?		

If **ALL** answers in Table C were **NO**, tick here

☐

Terminate

If **ANY** answers in Table C were **YES**, tick here

☐

Transport

**ONCE COMPLETE, LEAVE THIS FORM IN THE DESIGNATED AREA ON STATION**

## APPENDIX 7 - email relating to cost of ambulance provision

**From:** I  
**Sent:** 28 September 2016 07:20  
**To:** Matthew House  
**Subject:** Cost of a 24/7 double manned ambulance resource

Morning Matt

In relation to your request I can confirm that the average cost of a double manned ambulance is £72.00.

This includes all of the following aspects:-

- Direct Costs (staffing, medical and surgical equipment / consumables, fuel, costs we can directly allocate to a vehicle e.g. insurance etc)
- Indirect Costs (an example of what falls into this category are station costs, workshops, EOC, IMT)
- Overhead (this reflects a contribution to all the organisational structure, e.g. clinical audit, governance, HR, training, etc)

If I can be of any further assistance, please do not hesitate to get in touch  
With thanks

Head of Finance (Paramedic Emergency Service and Urgent Care)  
Ambulance Service NHS Trust