Prehospital critical care for out-of-hospital cardiac arrest: a complex intervention in a complex environment

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Abstract

Background

Prehospital critical care has the potential to improve the currently low survival rates following out-of-hospital cardiac arrest (OHCA). In some areas of the United Kingdom, prehospital critical care teams are dispatched to OHCA, while in others the standard of care of Advanced Life Support (ALS) is seen as sufficient. This thesis examines prehospital critical care for OHCA from different perspectives and aims to provide stakeholders in prehospital care with the information required to guide the funding and configuration of prehospital critical care for OHCA.

Methods

1. Qualitative analysis of stakeholders' views on research and funding of prehospital critical care. Data from focus groups and interviews of five stakeholder groups were analysed using the framework approach.

2. Economic analysis of ALS and prehospital critical care for OHCA. A decision analysis model of costs and effects of ALS for OHCA was created, using secondary data as well as data provided from relevant prehospital organisations. A range of possible effects of prehospital critical care for OHCA were simulated. A probabilistic sensitivity analysis was chosen to reflect the uncertainty of the underlying data.

3. Prospective multicentre observational analysis, comparing survival to hospital discharge in patients with OHCA who received prehospital critical care or ALS. Propensity score matching was used to adjust for confounding and bias, subgroup analysis in patients with witnessed OHCA with shockable rhythm and two sensitivity analyses (primary dispatch and multiple imputation datasets) were used.

4. Descriptive analysis of prehospital critical care interventions during and after OHCA. Frequencies of critical care interventions were analysed according to patient groups; a propensity score matching analysis examined the effect of treatment at a cardiac arrest centre in patients transferred to hospital.

Results

Stakeholders expressed strong and often opposing views on a variety of topics discussed in regards to prehospital research, prehospital critical care and funding strategies.

The current standard of care, Advanced Life Support (ALS) delivered by paramedics, was cost-effective at less than £20,000 per quality-adjusted life year (QALY) gained.

After propensity score matching to account for an imbalance in prognostic factors, survival to hospital discharge did not differ between patients with OHCA receiving prehospital critical care or ALS care. These results were stable throughout the subgroup and sensitivity analyses. In addition, prehospital critical care for OHCA is considerable more expensive than ALS and therefore highly unlikely to be cost-effective.

The reasons for this lack of clinical effectiveness of prehospital critical care can be likely found in the low frequency of interventions delivered and the relatively late arrival of critical care teams at the scene of an OHCA.

Stakeholders' considerations in regards to further funding of the complex intervention of prehospital critical care for OHCA will likely include additional factors such as social acceptability, available resources and the potential for indirect benefits.

Conclusions

This research provided a multi-faceted analysis of the complex intervention prehospital critical care for OHCA. The results can aid decision making in regards to future funding but also consider uncertainty in data analysis and the complex environment in which prehospital critical care is being delivered.

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Abbreviations

AED	Automated external defibrillator
ALS	Advanced Life Support
ATT	Average treatment effect on the treated population
BLS	Basic Life Support
CABG	Coronary artery bypass graft surgery
CCP	Critical care paramedic
CPC	Cerebral Performance Category
CPR	Cardiopulmonary resuscitation
DNAR	Do Not Attempt Resuscitation
ECA	Emergency care assistant
ECG	Electrocardiogram
ECMO	Extracorporeal membrane oxygenation
ED	Emergency department
ELST	Emergency Life-Saving Technician
EMS	Emergency Medical Services
GWAA	Great Western Air Ambulance
HCHS	Hospital and Community Health Services
HEMS	Helicopter Emergency Medical Services
ICER	Incremental cost-effectiveness ratio
ICNARC	Intensive Care National Audit and Research Centre
ICU	Intensive care unit
IV	Intravenous
JRCALC	Joint Royal Colleges Ambulance Liaison Committee
MCPR	Mechanical chest compressions
MLR	Multiple logistic regression
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NNT	Number needed to treat
OHCA	Out-of-hospital cardiac arrest
OHCAO Registry	Out-of-Hospital Cardiac Arrest Outcomes Registry
OR	Odds ratio
PCC	Prehospital critical care service
PCI	Percutaneous coronary intervention
PEA	Pulseless electrical activity
PHEA	Prehospital emergency anaesthesia
PICO	Population, intervention, comparator, outcomes
PICOS	Population, intervention, comparator, outcomes, study designs
PPI	Patient and public involvement
PSS	Personal social services
ROSC	Return of spontaneous circulation
RRV	Rapid response vehicle
RSI	Rapid sequence induction of anaesthesia
TTM	Targeted temperature management

UK	United Kingdom
USA	United States of America
VF	Ventricular fibrillation
VT	Ventricular tachycardia
WHO	World Health Organisation
WTP	Willingness-to-pay

Prologue

The treatment of patients with out-of-hospital cardiac arrest (OHCA) is the kind of healthcare intervention that galvanises Emergency Medical Services (EMS) providers. The stakes are high, the pace is fast and the mind is focused. Defibrillation, chest compression, Adrenaline and oxygen are provided while the team attempts to restart a patient's heart in a living room, bookstore or at the side of a road.

" ... death is the ultimate enemy, and I find nothing reproachable in those who rage mightily against the dying of the light." (Gould, 1985, pp.3-4)

The excited elation which follows a successful resuscitation of a patient with OHCA is only dampened by the frequent futility of such attempts. As others have noted, more healthcare, or *"raging mightily against the dying of the light"*, is probably not always the right strategy, particularly towards the end of an individual's lives (Gawande, 2014; Timmermanns, 1999). To quote Stephen Jay Gould again:

"when my skein runs out I hope to face the end calmly and in my own way." (Gould, 1985, p.4)

When caring for patients with OHCA, EMS providers enter patients' and their families' lives at a unique moment, with the power to save lives or to aid the family with the beginning of the grieving process. Either way, their actions have profound consequences. I hope this thesis can help EMS providers, organisations and funders to improve prehospital care for OHCA, by examining one potentially beneficial but complex intervention: prehospital critical care.

This thesis is dedicated to all EMS providers, who work long hours, who face adversity and who make difficult decisions on a daily basis. May you be fuelled by enthusiasm and comradery and may your practice be guided by evidence and compassion.

1. Introduction

The subject of this thesis is out-of-hospital cardiac arrest (OHCA) and whether a group of specially trained healthcare providers, prehospital critical care practitioners, can improve the outcome of this often-fatal condition. Before this question is addressed in the later chapters of this thesis, it is important to consider a number of questions.

- What is cardiac arrest and why is it an important healthcare issue?
- What are the current treatment options?
- What is prehospital critical care and how does it apply to cardiac arrest?
- What research underpins current and developing practice?

I will address these questions in the following sections to allow the reader to place both the condition and the intervention studied in this thesis in the relevant context.

1.1 Epidemiology of out-of-hospital cardiac arrest

Beginning a thesis with definitions of the condition in question might not invoke a notion of novelty or excitement in the reader. However, in the case of OHCA, a clear understanding of the definition is essential for the interpretation of existing research and wider issues surrounding the treatment of OHCA. Of particular concern is the difficult differentiation between a patient suffering from OHCA and a patient who is dying. In the latter case, inappropriate application of treatment for OHCA will be non-beneficial or even harmful. On the other hand, epidemiological studies have demonstrated extensively that OHCA is a major cause of preventable mortality and morbidity with overall low survival rates. Early identification and aggressive treatment gives patients with OHCA a small but significantly improved chance of survival.

1.1.1 Definitions of out-of-hospital cardiac arrest

cardiac arrest *(noun)*

A sudden, sometimes temporary, cessation of the heart's functioning

death *(noun)*

1. The action or fact of dying or being killed; the end of the life of a person or organism

2. The state of being dead

3. The permanent ending of vital processes in a cell or tissue

(English Oxford Living Dictionaries, 2017a and 2017b)

Much research, money, time and literally blood, sweat and tears have been spent on attempts to stop progression from cardiac arrest to death, as defined by the Oxford Dictionary. The cessation of the heart's functioning results in a lack of movement of blood throughout the body, which in turn leads to cell death from hypoxia and accumulation of products of metabolism in vital tissues such as brain, heart muscles or kidneys (Jentzer, Chonde and Dezfulian, 2015; O'Neil *et al.*, 2007). If untreated, a person in the state of cardiac arrest will usually suffer irreversible tissue damage and death within minutes (Dhanani *et al.*, 2014). Modern medicine differentiates between two main types of cardiac arrest, in-hospital and out-of-hospital, defined by the location of the person at the time of the cardiac arrest. Due to the differences in pathophysiology, treatment response and outcomes between out-of-hospital and in-hospital cardiac arrests, they are usually studied separately (Le Guen and Tobin, 2016). For the same reasons, cardiac arrest occurring in children is also generally described and treated as a separate entity (de Caen *et al.*, 2015). This thesis focuses exclusively on OHCA occurring in an adult population and the treatment of the condition by the emergency medical services (EMS), known in the United Kingdom (UK) as the ambulance service.

The English Oxford Living Dictionaries (2017b) definition of cardiac arrest poses important challenges to EMS providers and research in OHCA. What constitutes "*sudden"*? How do we recognise the "*cessation of the heart's functioning"*?

The World Health Organisation's (WHO) definition requires a cardiac arrest to occur within 1 hour of symptom onset for witnessed arrests, or within 24 hours of having been observed alive and symptom-free for unwitnessed arrests (Working Group on Ischemic Heart Disease Registers, 1969). While this definition allows suddenness to be measured, in reality it is often very difficult for the prehospital provider to establish this information reliably. Particularly in unwitnessed cardiac arrests this information is frequently unavailable, thus limiting the usefulness of the definition (Nichol and Baker, 2007). It also does not offer any further information on the recognition of cessation of the heart's functioning. A task force of the International Liaison Committee on Resuscitation (ILCOR) created a set of definitions relevant to OHCA, with the aim of providing a structured framework for research. The so-called Utstein definitions and data collection template for OHCA research were first published in 1991, after a meeting of relevant societies in the Utstein Abbey in Norway (Cummins, 1991). They have since been updated in 2004 and again in 2014 (Perkins *et al.*, 2015a). The Utstein criteria are used extensively in OHCA research and are further discussed in Section 1.4.2. See Box 1.1 for the Utstein definition of OHCA.

Box 1.1 The Utstein definition of out-of-hospital cardiac arrest (Perkins *et al.*, 2015a)

"Cardiac arrest is the cessation of cardiac mechanical activity as confirmed by the absence of signs of circulation. If an EMS provider or physician did not witness the cardiac arrest, he/she may be uncertain as to whether a cardiac arrest actually occurred."

EMS: Emergency Medical Services

The Utstein definition of OHCA avoids the problem of defining suddenness by not including any time limits. The absence of signs of circulation is not further described, but it is generally accepted that an unresponsive patient with no palpable pulse and/or absence of normal breathing is in cardiac arrest (Soar *et al.*, 2015). The Utstein definition has the advantages of being easy to apply and being very sensitive (i.e. not missing any cardiac arrests). The disadvantage however, is a lack of specificity, as discussed in the next section.

1.1.2 Not all out-of-hospital cardiac arrests are the same

The established Utstein definition of OHCA includes any person who displays no clinical signs of circulation, and whose heart is therefore assumed to have stopped functioning. This wide definition can, in practice, include a range of patient groups:

1. Patients suffering a sudden cardiac arrest, triggered by an acute physiological crisis, such as a heart attack, trauma or other pathology (see Section 1.1.3). With effective early treatment, this patient group has a considerable chance of recovery and meaningful survival (Nichol *et al.*, 2015).
2. Patients whose heart has stopped functioning due to non-acute processes, such as advanced age or terminal illness. While patients in this group can be successfully resuscitated, meaningful survival is rarer due to the limitations of the underlying conditions (Andrew *et al.*, 2014; Sehatzadeh, 2014).
3. Patients who have completed the dying process to an irreversible stage. The actual moment of death in this group is often unwitnessed, and patients are found unresponsive with signs incompatible with life (Madea, 2016).
4. Patients who had an episode of *"absence of signs of circulation"* recognised and treated by a bystander which has resolved by the time the first EMS provider is with the patient. In the absence of defibrillation by a public access defibrillator, these events can be due, for example, to a vasovagal syncope, a low blood sugar episode in a diabetic person or drug intoxication (Reed and Gray, 2006). As the Utstein definition describes, there is a significant uncertainty for some of these cases as to whether OHCA actually occurred.

The focus of this thesis and the majority of research in OHCA is the first patient group, as they are the most likely to benefit from the prehospital treatments described in Sections 1.2 and 1.3 (Hamilton *et al.*, 2016; McNally *et al.*, 2011). Unfortunately, this group can be difficult to distinguish clinically from groups two and three, especially for the EMS provider who needs to make treatment decisions within seconds, if the patient is to benefit from interventions.

This is a methodological challenge for all OHCA research, as inclusion or exclusion of cases depends heavily on this initial EMS provider assessment. In a study by Dull *et al.* (1994), approximately one quarter of patients with OHCA suffered from severe chronic illness, with significantly lower survival rates. Regional differences in population health therefore have significant effects on reported survival rates in individual EMS systems (Sehatzadeh, 2014).

The same can be said for the implementation of Do Not Attempt Resuscitation (DNAR) orders, which are more frequently used in the elderly and chronically ill. Somewhat ironically, a system-wide method of improving reported survival rates from OHCA would be to increase the number DNAR orders and therefore reduce futile resuscitation attempts (Nehme *et al.*, 2014). Frequency of DNAR orders and how they are actioned by EMS providers vary significantly around the world and have also undergone considerable changes over the last 20 years (Fallahi *et al.*, 2016; Grudzen *et al.*, 2009; Burns *et al.*, 2003).

Patients in the third group, with irreversible signs of death, are a surprisingly frequent cause of EMS deployment for OHCA, ranging from approximately 30% (Grudzen *et al.*, 2010) to 50% (Andrew *et al.*, 2014) of all activations for OHCA in an American and Australian EMS system, respectively. Most EMS systems therefore have clear guidelines on the recognition of irreversible signs of death and subsequent withholding of resuscitation (Brown *et al.*, 2016). These guidelines vary between EMS systems and also in their implementation by prehospital providers within single EMS systems (Lockey, 2002). The concern is that, through the inclusion of cases of death from non-acute processes and irreversible death, studies overestimate the true incidence of (sudden) OHCA, while underestimating survival rates (Nishiyama *et al.*, 2014). In a recent study from Australia, the exclusion of cases where resuscitation was commenced but then terminated, due to irreversible signs of death or DNAR orders, resulted in a relative reduction of cardiac arrest incidence of 18.1% and increased reported survival rates from 13.2% to 16.2% (Nehme *et al.*, 2014).

Finally, cases of bystander-recognised OHCA that have resolved by the time of arrival of the first EMS resource raise similar issues. In the absence of defibrillation with a public access automated external defibrillator (AED), many of these patients will not actually have suffered a cardiac arrest, resulting in potential overestimation of survival rates after cardiac arrest (Sayre *et al.*, 2004).

Publications discussing the epidemiology of OHCA usually refer to the event of sudden or unexpected cessation of the heart's functioning and use stringent definitions of OHCA. These findings are summarised in the next section. It is worth noting that the cohorts of OHCA patients described in epidemiological studies are not necessarily the same as those studied in research that examines treatment and outcomes from OHCA, where the less specific Utstein definition of OHCA is frequently used (Engdahl *et al.*, 2002).

1.1.3 Incidence and aetiology of out-of-hospital cardiac arrest

A systematic review and meta-analysis by Atwood *et al.* (2005) calculated the incidence of EMS-treated OHCA in Europe as 38 per 100,000 person years, which translates to 275,000 cases annually. Of these, 89.3% or 246,000 patients will die every year. The same methods were applied to data from the United States of America (USA) and results were similar with an incidence of 54.99 per 100,000 person years and survival rates of 8.4% (Rea *et al.*, 2004).

Evidence from low- or middle-income countries is sparse, but it is expected that the incidence of OHCA will increase over time, as successful treatments of mainly communicable diseases increase the life expectancy of the population in these countries (Vedanthan, Fuster and Fischer, 2012).

Approximately 65% to 80% of sudden OHCAs in adults in developed countries are thought to be of cardiac aetiology (Soo, Gray and Hampton, 2001; Uretsky *et al.*, 2000; Kuisma and Alaspaa, 1997). This term comprises a number of cardiovascular pathologies, summarised in Table 1.1. Of these, ischaemic heart disease is by far the most common pathology, responsible for approximately 80% of OHCAs of cardiac aetiology (Davies, 1992; Myerburg, 1987).

Table 1.1 Common causes of out-of-hospital cardiac arrest of cardiac aetiology (Nichol and Baker, 2007; Engdahl *et al.*, 2002)

Cardiac causes (representative conditions)
Coronary atherosclerosis (myocardial infarction, angina)
Heart failure (left or right ventricular failure)
Valvular heart disease (aortic stenosis, mitral insufficiency)
Ventricular hypertrophy (acquired or congenital)
Congenital heart disease (coronary artery abnormalities, complex defects)
Conduction abnormalities (Wolff-Parkinson-White syndrome, Lev's disease)
Infiltrative cardiomyopathy (sarcoidosis, haemochromatosis)
Pericardial disease (pericarditis, pericardial tamponade)
Cardiac tumours (myxoma)

The remaining causes of OHCA are listed in Table 1.2 and can be broadly divided into traumatic and non-cardiac medical causes. Traumatic injuries are usually acute, obvious events, which are readily identifiable by EMS providers. On the other hand, non-cardiac medical causes of OHCA can be difficult to distinguish clinically from OHCA due to cardiac causes.

Table 1.2 Common non-cardiac causes of out-of-hospital cardiac arrest (Nichol and Baker, 2007; Engdahl *et al.*, 2002)

Traumatic causes (representative conditions)
Major trauma (haemorrhagic shock, impact apnoea)
Drowning
Asphyxia (strangulation, noxious gases)
Non-cardiac medical causes (representative conditions)
Vascular (aortic dissection, pulmonary embolism)
Neurological (cerebrovascular event, seizures)
Infectious (severe sepsis, myocarditis)
Respiratory (bronchospasm, aspiration, tension pneumothorax)
Immunological (anaphylactic shock, angioedema)
Toxic substances (illicit and pharmaceutical drugs)
Electrolyte/metabolic disturbances (diabetic ketoacidosis, hyperkalaemia)
Other (vasculitis, heat stroke)

This thesis focuses on adult patients with OHCA of either cardiac aetiology or medical causes of non-cardiac aetiology, because traumatic OHCA can be seen as the end-point of a very different acute disease process, requiring different treatments (Rabinovici and Bugaev, 2014).

Given the dominance of OHCA of cardiac aetiology and its strong association with age, it is not surprising that the incidence of OHCA increases exponentially with age (de Vreede-Swagemakers *et al.*, 1997). The incidence of OHCA is also higher in men than in women and higher in people of non-white ethnicity, but a considerable degree of these variances can be explained by variations in risk factors for OHCA (McNally *et al.*, 2011; Kannel and McGee, 1985).

1.1.4 Risk factors for out-of-hospital cardiac arrest

Risk factors relating to OHCA are important in two considerations. There are factors that put an individual at risk of suffering an OHCA and risk factors that determine the risk of dying after an OHCA has occurred. This section will discuss risk factors for suffering an OHCA, while the prognostic factors for survival following OHCA will be discussed in more detail in Section 1.3.2. Of note, many factors increase both the risk of experiencing an OHCA and the risk of dying from OHCA (Nichol and Baker, 2007).

The single largest risk factor for sudden OHCA is coronary artery disease, resulting in cardiac ischaemia or myocardial infarction, which in turn triggers an OHCA (Davies, 1992; Myerburg, 1987). The risk factors for coronary artery disease in developed countries are well established and include age, hypertension, elevation of serum cholesterol levels, diabetes, genetic factors, obesity and smoking (Levy *et al.*, 1990). Despite this well-established causal chain from risk factors to OHCA, for a large proportion of events, prevention is difficult. OHCA is estimated to be the first presentation of coronary artery disease in 40-60% of patients with OHCA (de Vreede-Swagemakers *et al.*, 1997; Kannel and McGee, 1985). Furthermore, the risk factors derived from the Framingham Heart Study are highly applicable on a community level but show poor performance in predicting myocardial infarction or OHCA in individuals (van Staa *et al.*, 2014). In fact, the majority of OHCAs occur in the low-risk general publication, simply because this group by far outnumbers the relatively small group of high-risk individuals (Campbell *et al.*, 2007; Kannel and McGee, 1985).

Other risk factors have been studied, including environmental, social and behavioural factors, but it is often unclear if they influence the risk of OHCA independently, or act as confounders or mediators. OHCA occurs more frequently on Mondays and in the morning, however, this might be due to people dying without being witnessed and the body not being discovered until daily activity resumes (Gruska *et al.*, 2005; Herlitz *et al.*, 2002). There are clear disparities in OHCA incidence across geographical regions, socio-economic gradients and race, associated with differences in health behaviour, access to health care and different distributions of coronary artery disease risk factors (Singh and Siahpush, 2002; Becker *et al.*, 1993). While OHCA is more likely to occur during or shortly after strenuous physical exercise, regular exercise exerts a protective effect (Mittleman *et al.*, 1993). Smoking, excessive alcohol intake or the use of illicit drugs, particularly Cocaine, are associated with an increased risk of OHCA, independent of coronary artery disease (Nichol and Baker, 2007). More recent research has shown interest in and potential benefit from better understanding of cellular and genetic risk factors for OHCA. While genetic studies have identified an inherited risk of OHCA in certain families and have the potential to discover further risk factors, they do not play any role in prevention of OHCA in the general population today (Spooner *et al.*, 2001; Jouven *et al.*, 1999).

Risk factors for OHCA not due to coronary artery disease depend on, and are specific to, the underlying condition causing the OHCA. The conditions outlined in Tables 1.1 and 1.2 affect different populations for different reasons and a detailed discussion of the associated risk factors is beyond the scope of this thesis (Nichol and Baker, 2007).

Despite our extensive knowledge of population-level risk factors for suffering sudden OHCA, we are still unable to predict when and where an individual at risk will experience an OHCA. If OHCA occurs, it usually does so, by the very nature of the term, outside a monitored medical environment. The fact that severe pathophysiological changes occur within minutes of OHCA poses a challenge for EMS systems providing timely treatment, but also for research into the pathophysiology of OHCA.

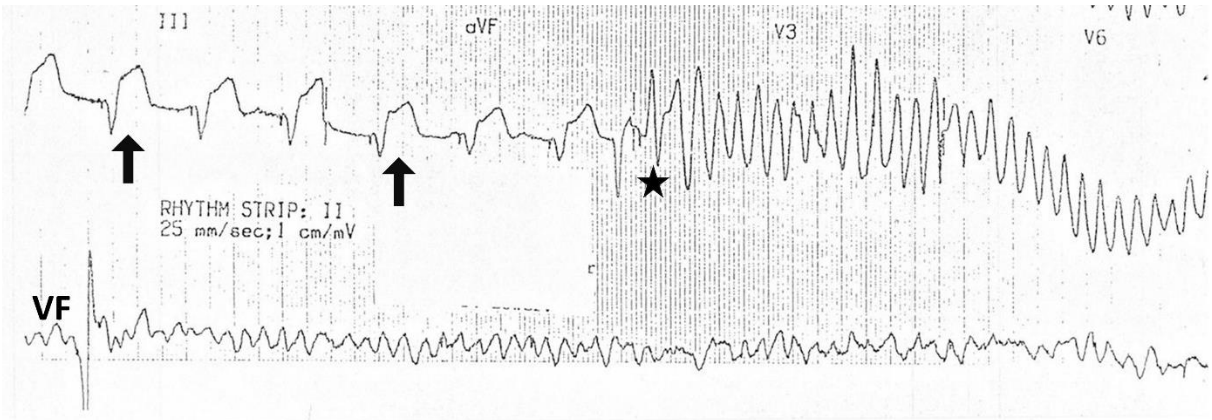
1.1.5 Pathophysiology of out-of-hospital cardiac arrest

As most patients who suffer an OHCA are not attached to cardiac monitoring at the time of the event, description of the pathophysiological process relies largely on extrapolation from autopsy studies or small subgroups of OHCA occurring in the presence of EMS providers (Nichol and Baker, 2007). Significant coronary artery disease was identified on post-mortem examinations in up to 80% of deaths from OHCA, but was also found in 12% of deaths unrelated to OHCA (Davies, 1992; Davies, 1981). A clinical model of OHCA suggests that an underlying structural heart disease (see common examples in Table 1.1) coincides with dynamic influences, such as myocardial ischaemia or reperfusion, hypoxia, acidosis, electrolyte imbalance, catecholamine excess, autonomic dysfunction, toxins or arrhythmogenic drugs (Nichol and Baker, 2007; Myerburg *et al.*, 1989). The resulting instability in myocardial electrical conduction leads to malignant ventricular tachy-arrhythmias, most frequently ventricular fibrillation (VF).

The two other cardiac rhythms most commonly identified on electrocardiograms (ECGs) during OHCA are pulseless electrical activity (PEA) and asystole (Hawkes *et al.*, 2017). Each of the three groups of cardiac rhythms found during OHCA (VF, PEA and asystole) have a distinct pathophysiology, with important consequences for treatment and prognosis.

VF is estimated to be the cause of 80-90% of OHCAs of cardiac aetiology (Holmberg, Holmberg and Herlitz, 2000a). See Figure 1.1 for the ECG of a patient with myocardial infarction with subsequent ventricular tachycardia, deteriorating into VF. The unorganised electrical activity, the hallmark of VF, corresponds to an absence of coordinated heart muscle activity with loss of circulation due to cardiac arrest. If untreated, VF decreases in magnitude and eventually deteriorates into asystole, the absence of any electrical activity in the heart (Holmberg, Holmberg and Herlitz, 2000a). During this period of OHCA, chest compressions by bystanders or EMS providers can provide potentially life-saving blood flow to the patient's organs and can also slow the deterioration from VF to asystole (Cummins *et al.*, 1985). As long as VF is present, this chaotic electrical activity can be restored to organised electrical complexes, and often a return of spontaneous circulation, through the use of external electrical defibrillation (Hallstrom *et al.*, 2004). These two elements of the treatment of OHCA (chest compressions and defibrillation) are both crucial and highly time critical and will be further discussed in the next section.

Figure 1.1 12-lead ECG and subsequent rhythm strip (Burns, 2017), with permission from M. Cadogan, lifeinthefastlane.com



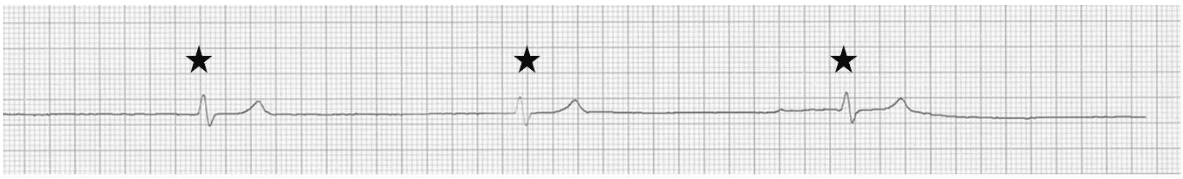
Arrows: Regular QRS complexes (paced) with ST-elevation. Star: Beginning of polymorphic ventricular tachycardia. VF: Subsequent ventricular fibrillation.

The incidence of VF in studies of OHCA depends on many factors, including the definition of cardiac arrest used, population characteristics, bystander cardiopulmonary resuscitation (CPR) and EMS response times (Nishiyama *et al.*, 2014). In the pilot study to this PhD thesis, VF was the first cardiac rhythm recorded by EMS providers in 28% of cases. Another 50% of cases presented in asystole, the presenting cardiac rhythm in the remaining 22% was PEA (von Vopelius-Feldt, Coulter and Benger, 2015). These findings are consistent with research from other countries, such as Norway and Germany (Olasveengen *et al.*, 2009; Estner *et al.*, 2007).

Given that asystole is the most common presenting cardiac rhythm in many studies of OHCA, there is a surprising lack of research into its pathophysiology (Ornato and Peberdy, 1996). Asystole, when present, is generally considered a consequence of OHCA, rather than the cause (Engdahl *et al.*, 2002). It is thought that the majority of OHCA are caused by either VF or PEA, which then deteriorate into asystole (Silfvast, 1991). This is supported by the fact that survival is rare once asystole has occurred, especially in unwitnessed OHCA or in elderly patients (Engdahl *et al.*, 2000). One of the major practical implications of asystole in OHCA is the recognition of irreversible death (in combination with other factors) by EMS providers and subsequent cessation of resuscitation (Brown *et al.*, 2016).

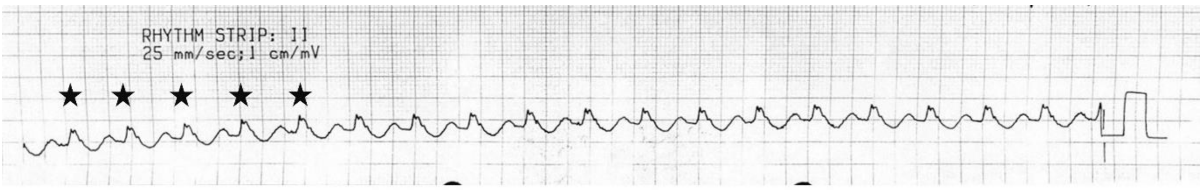
Pulseless electrical activity is a clinical description of OHCA where no pulse is palpable by the EMS provider, but cardiac ECG monitoring shows organised electrical complexes which are compatible with cardiac contractions. See Figures 1.2 and 1.3 for examples of ECGs which might be found in PEA OHCA.

Figure 1.2 ECG rhythm strip with occasional organised QRS complexes (Burns, 2017), with permission from M. Cadogan, lifeinthefastlane.com



Stars: Organised QRS complexes, compatible with cardiac contractions. Infrequent and broad QRS complexes are commonly seen in pseudo-PEA or true PEA (ECG recorded after prolonged resuscitation in this case).

Figure 1.3 12-lead ECG with tachycardia and right bundle branch block (Burns, 2017), with permission from M. Cadogan, lifeinthefastlane.com



Stars: Organised QRS complexes (only the first five are marked), compatible with cardiac contractions. Heart rate of approximately 120/min would suggest normotensive PEA as underlying cause (pulmonary embolism in this case).

To better understand the mechanisms of PEA OHCA, it is useful to further divide PEA into normotensive PEA, pseudo-PEA and true PEA, and to relate these three groups to the causes of cardiac arrest listed in Tables 1.1 and 1.2 (Aufderheide, 2007). Normotensive PEA is characterised by normal baseline cardiac contractions but absence of a pulse and is caused by either mechanical obstruction of blood flow (cardiac tamponade, tension pneumothorax) or severe reduction of blood returning into the heart (haemorrhage, sepsis, pulmonary embolism) (Aufderheide, 2007; Charlap *et al.*, 1989). In pseudo-PEA, myocardial contractions are also present but too weak to generate a palpable pulse (Paradis *et al.*, 1992). Causes include myocardial infarction or heart failure, toxic substances, metabolic or electrolyte abnormalities and hypoxia (Aufderheide, 2007). Finally, true PEA is defined as complete absence of cardiac contraction, despite ongoing electrical cardiac activity. True PEA is thought to be the consequence of the severe global hypoxia, acidosis and increased vagal tone that develop within minutes of OHCA due to VF, normotensive or pseudo-PEA (Jennings and Reimer, 1981), with blood flow through the coronary arteries being severely impaired during OHCA, rendering the heart muscles non-contractile (Sanders, Ogle and Ewy, 1985). Like VF, all three types of PEA OHCA will eventually deteriorate into asystole unless successfully treated.

The three groups of cardiac arrest rhythms presented in this section, ventricular tachycardia/VF, PEA and asystole, have important implications for the treatment of OHCA but also for the survival of individual patients. While most people would arguably be more interested in survival than in treatment, in the case of OHCA the first cannot happen without the second. Without treatment, death from OHCA is inevitable. With treatment in modern EMS and hospital systems, reported survival rates after OHCA vary from 5% to 15% (von Vopelius-Feldt, Coulter and Benger, 2015; Yasunaga *et al.*, 2010; Estner *et al.*, 2007; Stiell *et al.*, 1999). In the next section I will describe the treatments and interventions required for the so-called Chain of Survival, before returning to the question of who survives OHCA and how.

1.2 Treatment of out-of-hospital cardiac arrest

Resuscitation of a patient in cardiac arrest is a dramatic event for healthcare providers, bystanders or relatives and, of course, the patient whose life depends on a successful result. This section describes the transition from early experimental resuscitations to the modern, highly standardised interventions of Basic and Advanced Life Support. Timely availability of interventions is a key concept, reflected in the so-called Chain of Survival, which extends from bystander and EMS to hospital care.

1.2.1 History of resuscitation

Until the 18th century, death was generally considered an irreversible event. Any attempt to revive a person after death had occurred would have been considered blasphemous or scientifically impossible (Baker, 1971). With the general advances of science and secularism, the origins of modern resuscitation can be found in European cities during the period of

Enlightenment (Eisenberg, Baskett and Chamberlain, 2007). Of course, death from cardiovascular disease, which is the leading cause of cardiac arrest in the developed world today, would have been a rarity in the 18th century (McNally *et al.*, 2011). People died from trauma, infections, drowning or smoke inhalations from fire (Virgoe, 2005). While death due to the first two conditions was rightly considered irreversible at the time, early resuscitation efforts focused particularly on victims of drowning and asphyxia from noxious gases. It is therefore not surprising that the first organised efforts of resuscitation from cardiac arrest developed in cities like Amsterdam, Venice, London and Paris and concentrated on clearing the airway and ventilating the lungs of the victim (Cary, 1918; Fothergill, 1745). This focus on airway and ventilation in resuscitation attempts remained largely unchanged for the next 200 years. During this time, a plethora of methods competed for the status of being the most effective, based on often unverified case reports or basic scientific arguments (Karpovich, 1953).

Only in the early twentieth century did a new resuscitation technique gain widespread recognition. Manual compression of the chest was successful in restoring the circulation of patients suffering cardiac arrest as a consequence of anaesthesia. This technique resulted in full recovery of patients (and even completion of the planned surgery immediately after the event) (Kouwenhoven, Jude and Knickerbocker, 1960). In the early 1960s, the most effective methods for ventilation (either mouth-to-mouth ventilation or using a self-inflating bag) were combined with manual chest compressions, named cardiopulmonary resuscitation (CPR) and quickly became the standard of resuscitation care (National Research Council, 1966).

The final intervention needed to complete the foundation of modern resuscitation practices for cardiac arrest was defibrillation. Scientists and physicians had developed a keen (and sometimes hazardous) experimental interest in the healing effects of electricity for all kinds of ailments in the late 19th century (Schechter, 1983). However, for electricity to become a central pillar of resuscitation, three key steps were required. The first step was the recognition of VF as an (by then increasingly common) cause of cardiac arrest (McWilliam, 1889). From here, it took 60 years for defibrillation to be recognised as potential treatment for VF and to be successfully used in a human (Beck, Pritchard and Feil, 1947).

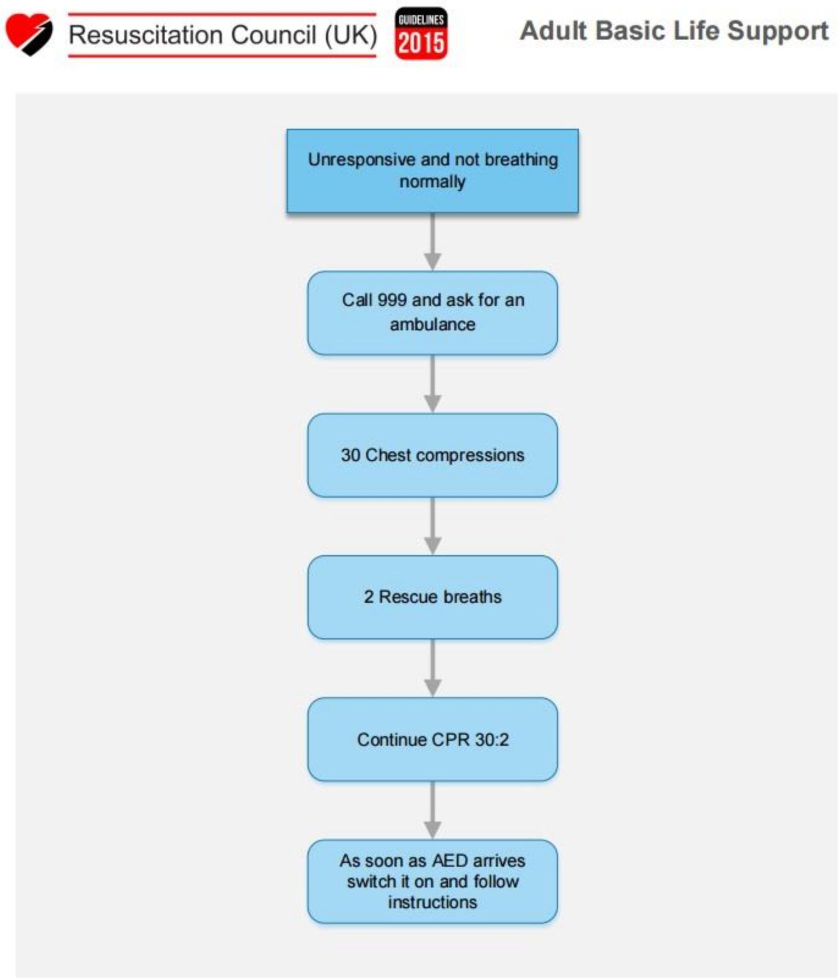
Finally, for the technique to become widespread, technology needed to advance. In 1962, Lown, Amarasingham and Neuman (1962) designed the first portable defibrillator capable of creating an electric shock strong enough to successfully achieve external cardiac defibrillation. Airway management, ventilation, manual chest compression and defibrillation quickly became the foundation of modern prehospital care for OHCA, in the form of Basic or Advanced Life Support.

1.2.2 Basic and Advanced Life Support

For educational and logistic reasons, the therapeutic interventions for OHCA have been standardised into two levels of care, Basic Life Support (BLS) and Advanced Life Support (ALS) (Nolan *et al.*, 2015a). The definitions of BLS and ALS are internationally recognised with only minimal, if any, differences (Link *et al.*, 2015; Soar *et al.*, 2015).

BLS can be provided by lay persons or EMS providers with minimal training and equipment (Kleinman *et al.*, 2015). The emphasis lies on high-quality manual chest compressions, with minimal interruptions (Christenson *et al.*, 2009). Chest compressions can be supplemented with ventilation at a ratio of 30 compressions to two breaths, either through the mouth-to-mouth method, or, for EMS providers, with a simple bag-valve-mask device (Kleinman *et al.*, 2015). Treatment of VF through defibrillation used to be considered an advanced intervention. With the availability of automated external defibrillators (AEDs), designed to be used with minimal or no training, defibrillation can now be considered part of the BLS standard, sometimes referred to as BLS+D in research (Strohle *et al.*, 2014). See Figure 1.4 for a summary of BLS interventions for OHCA.

Figure 1.4 Adult Basic Life Support for cardiac arrest (Resuscitation Council (UK), 2015), with permission from Resuscitation Council (UK)



CPR: Cardiopulmonary resuscitation, AED: Automated external defibrillator

BLS will ideally commence with early bystander CPR, which will then be continued by prehospital providers on arrival at the scene. There is good evidence linking early CPR and also the quality of CPR to increased survival (Holmberg, Holmberg and Herlitz, 2000b; Gallagher, Lombardi and Gennis, 1995). While lung ventilation via the mouth-to-mouth method or a bag-valve-mask device is also part of BLS, there is little evidence to support this practice (Bohm *et al.*, 2007) and consequently the most recent guidelines of the European Resuscitation Council de-emphasise its importance (Perkins *et al.*, 2015b).

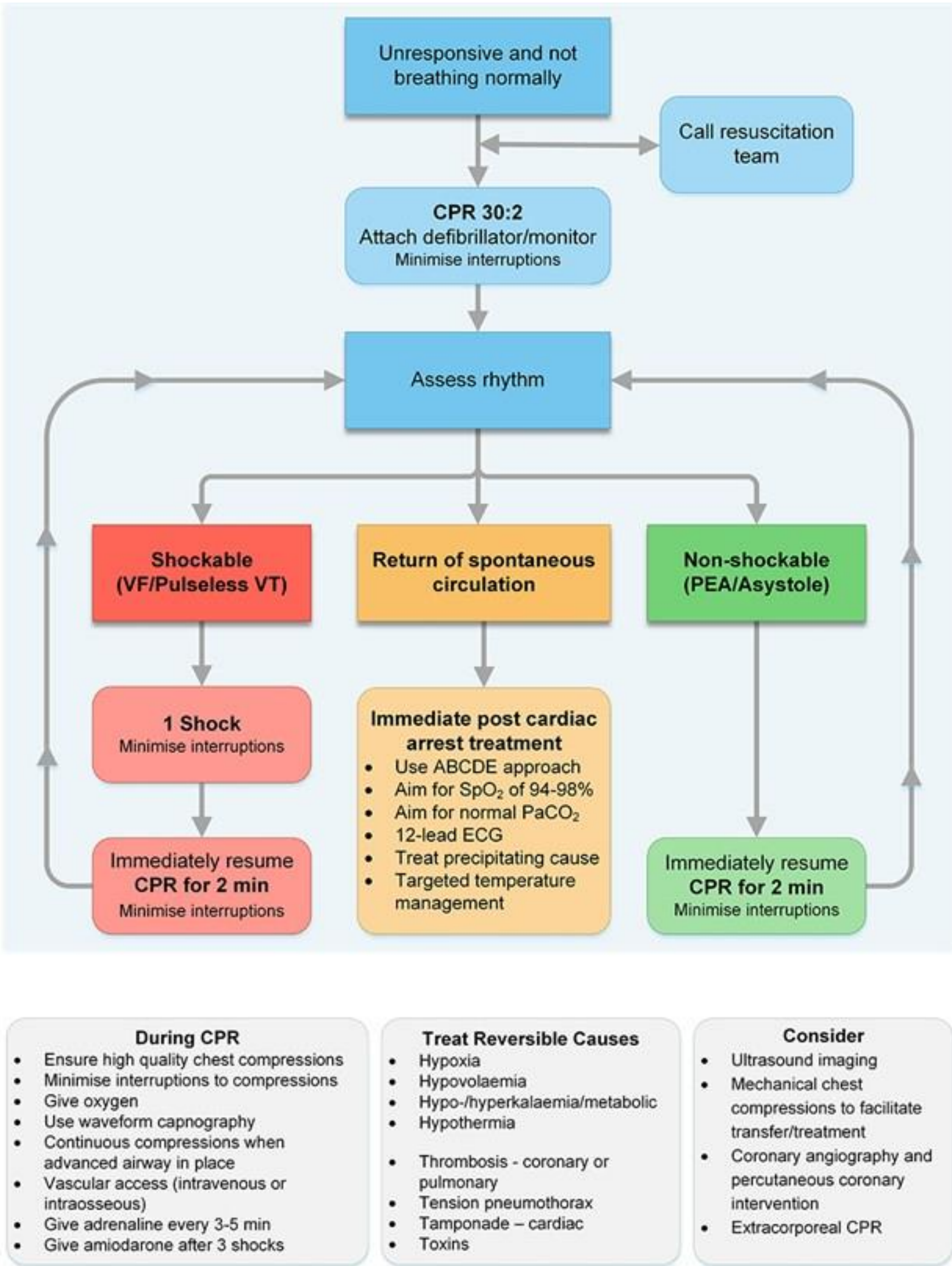
ALS combines the interventions of BLS (CPR, defibrillation) with advanced airway management, intravenous medications, consideration of reversible causes of cardiac arrest and treatment recommendations after return of spontaneous circulation (Soar *et al.*, 2015). See Figure 1.5 for an overview of the ALS algorithm.

ALS is the standard of care for OHCA in most European and North American EMS systems and is provided by paramedics, prehospital nurses or doctors (Black and Davies, 2005; Langhelle *et al.*, 2004; Pozner *et al.*, 2004). The focus remains on high-quality CPR and defibrillation of a shockable rhythm, but in addition delivery of oxygen and advanced airway management with either a supraglottic airway device or tracheal intubation are recommended (Soar *et al.*, 2015). However, clear evidence to support benefit from advanced airway management is lacking and there are concerns that these airway interventions may distract providers from the delivery of high quality CPR and defibrillation (Lockey and Lossius, 2014; Wang *et al.*, 2009).

Similar limitations apply to the second addition of ALS over BLS; administration of intravenous Adrenaline and Amiodarone. While Adrenaline is thought to improve coronary artery blood flow during CPR (Meybohm *et al.*, 2007), studies have also raised the possibility of harm being caused by the increased organ oxygen demand caused by excess Adrenaline (Halvorsen *et al.*, 2015). A randomised controlled trial and a systematic review both failed to demonstrate improved survival after OHCA with Adrenaline administration (Atiksawedparit *et al.*, 2014; Jacobs *et al.*, 2011). More recently, a large randomised controlled trial of Adrenaline during OHCA, undertaken in the UK, showed increased rates of survival, when compared to placebo (3.2% and 2.4%, respectively). However, this increase in survival was largely due to more patients surviving with moderate to severe disability in the Adrenaline arm of the trial (Perkins *et al.,* 2018). Amiodarone is thought to improve rates of successful defibrillation of shockable OHCA rhythms, but a recent randomised controlled trial showed only a minor benefit in a subgroup of patients with witnessed shockable OHCA (Kudenchuk *et al.*, 2014). A more recent systematic review found no evidence of improved survival (Tagami, Yasunaga and Yokota, 2017).

The third mainstay of ALS is the consideration of reversible causes of PEA OHCA, referred to as the four H's and T's (Figure 1.5, grey box, bottom centre). While the four H's and T's can serve as a useful reminder for prehospital providers during a stressful resuscitation, the frequency of causes which are reversible in the prehospital environment is very low, calling into question the actual impact on patients (Beun *et al.*, 2015).

Figure 1.5 Adult Advanced Life Support for cardiac arrest (Resuscitation Council (UK), 2015), with permission from Resuscitation Council (UK)



CPR: Cardiopulmonary resuscitation, VF: Ventricular fibrillation, VT: Ventricular tachycardia, PEA: Pulseless electrical activity, ECG: Electrocardiogram

Given the lack of proven benefit of three (advanced airway management, intravenous medication, consideration of reversible causes) of the four pillars of ALS in addition to BLS, it is perhaps not surprising that a recent, large retrospective registry analysis did not show improved survival rates after OHCA when comparing prehospital ALS to BLS (Sanghavi *et al.*, 2015). Other than the ALS interventions described above, a number of additional interventions for OHCA have been tested over the last decades, with similar results. See Figure 1.6 for a list of interventions which have been found to have no or only potential benefit during OHCA (Jentzer *et al.*, 2016).

Figure 1.6 Table by Jentzer *et al.* (2016), with permission from Annals of Emergency Medicine (license number 4083670613617)

Intervention	Effect on Outcomes	Best Evidence*
Compressions-only CPR	No benefit	Practice guidelines[12]; randomized trial[13]
Mechanical chest compressions	No benefit	Meta-analysis[14]
Impedance threshold device	No benefit	Meta-analysis[15]
Active compression/decompression	No benefit	Meta-analysis[16]
Delayed vs immediate CPR	No benefit	Meta-analysis[18]
Single vs multiple stacked shocks	No benefit	Practice guidelines[7]
Advanced airway placement	Uncertain	Meta-analysis[23]; observational study[22]
Intravenous line placement	No benefit	Randomized trial[24]
Epinephrine vs placebo	No benefit, possible harm	Meta-analysis[25]; observational studies[26,27]
High vs standard epinephrine dose	No benefit	Meta-analysis[28]
High-dose epinephrine vs high-dose norepinephrine	No benefit	Randomized trial[29]
Epinephrine vs vasopressin	No benefit	Meta-analyses[30,31]
Vasopressin+corticosteroids+epinephrine vs epinephrine alone	Possible benefit	Randomized trial[32]
Amiodarone vs lidocaine	Possible benefit	Meta-analysis[33]
Amiodarone vs nifekalant	Possible benefit	Meta-analysis[33]
Lidocaine vs placebo	Uncertain	Meta-analysis[33]; observational study[34]
Amiodarone vs placebo	No benefit	Meta-analysis[33]
Atropine vs placebo	No benefit	Observational study[35]
Aminophylline vs placebo	No benefit	Randomized trial[36]
Sodium bicarbonate vs placebo	Uncertain	Observational studies[37-39]
Magnesium sulfate vs placebo	No benefit	Practice guidelines[5]
Calcium chloride vs placebo	Uncertain	Practice guidelines[5]
Extracorporeal CPR vs conventional CPR	Possible benefit	Meta-analysis (observational studies)[40]; observational studies[41,42]
Out-of-hospital cooling	No benefit	Meta-analysis[43]

*All meta-analyses include randomized trials unless otherwise noted.

CPR: Cardiopulmonary resuscitation

1.2.3 Treatment options after successful resuscitation

Through the combined efforts of bystanders and prehospital providers, an increasing number of patients are resuscitated to achieve a return of spontaneous circulation (ROSC), which clinically manifests as a palpable pulse and/or signs of life (Sporer *et al.*, 2017). ROSC after BLS/ALS resuscitation occurs in 10% to 30% of OHCA cases but of these, only 30% to 50% survive to hospital discharge (Sporer *et al.*, 2017; Do Shin *et al.*, 2012; Jacobs *et al.*, 2011).

There is an increasing interest in optimising post-ROSC care, which is also reflected in the ALS algorithm in Figure 1.6. The ALS recommendations include the generic ABCDE approach to the critically ill patient, which aims to stabilise vital parameters and normalise organ function. It includes a set of examinations, observations, investigations and interventions for each of the five categories: airway; breathing; circulation; disability; exposure (Wyatt *et al.*, 2012). While this widely practiced approach is undoubtedly appropriate and useful, it is worth noting that it is largely based on common sense and immediate individual vital sign feedback loops rather than rigorous scientific evaluation (Nutbeam, 2013).

The recommendations also include a number of interventions specific to OHCA patients with ROSC, namely ultrasound imaging, targeted temperature management (TTM) and percutaneous coronary intervention (PCI) (Soar *et al.*, 2015). Early focused ultrasound imaging can not only aid therapy and decision making during OHCA but also helps to optimise the treatment of cardiovascular shock commonly present in post-ROSC patients (Jentzer *et al.*, 2016; Chin *et al.*, 2013). Ultrasound machines have only recently become lightweight and small enough to be used in the prehospital environment and evidence of actual patient benefit is so far lacking. Given the significant costs and unclear benefits, prehospital ultrasound is currently only used by a small number of EMS providers (Taylor *et al.*, 2014).

TTM and early PCI are delivered most frequently at receiving hospitals labelled cardiac arrest centres, receiving high numbers of patients with ROSC after OHCA. While it is not fully understood which of these three aspects, TTM, PCI and/or high volume of post-OHCA patients, is causally linked to increased survival, the evidence for a combination of these factors seems consistent (Dumas *et al.*, 2016; Kern, 2015; Nielsen *et al.*, 2013). The recently published document *Resuscitation to Recovery - A National Framework to improve care of people with out-of-hospital cardiac arrest (OHCA) in England* (OHCA Steering Group, 2017) has been endorsed by a number of relevant professional bodies in the UK. It recommends (OHCA Steering Group, 2017, p.25):

"All patients with ROSC should be taken to a designated 'cardiac arrest centre' that has expertise in the management of OHCA and has round-the-clock access to all relevant clinical services, including a cardiac catheter laboratory and an intensive care unit (ICU)."

The document also recommends that the Chain of Survival for OHCA should be "*embedded in public consciousness and into clinical pathways and protocols"* (OHCA Steering Group, 2017, p.7). See Figure 1.7 for the internationally recognised concept of the Chain of Survival, which is discussed in more detail in the next section.

1.2.4 The importance of time and the Chain of Survival

Figure 1.7 The Chain of Survival (Resuscitation Council (UK), 2015), with permission from Resuscitation Council (UK)

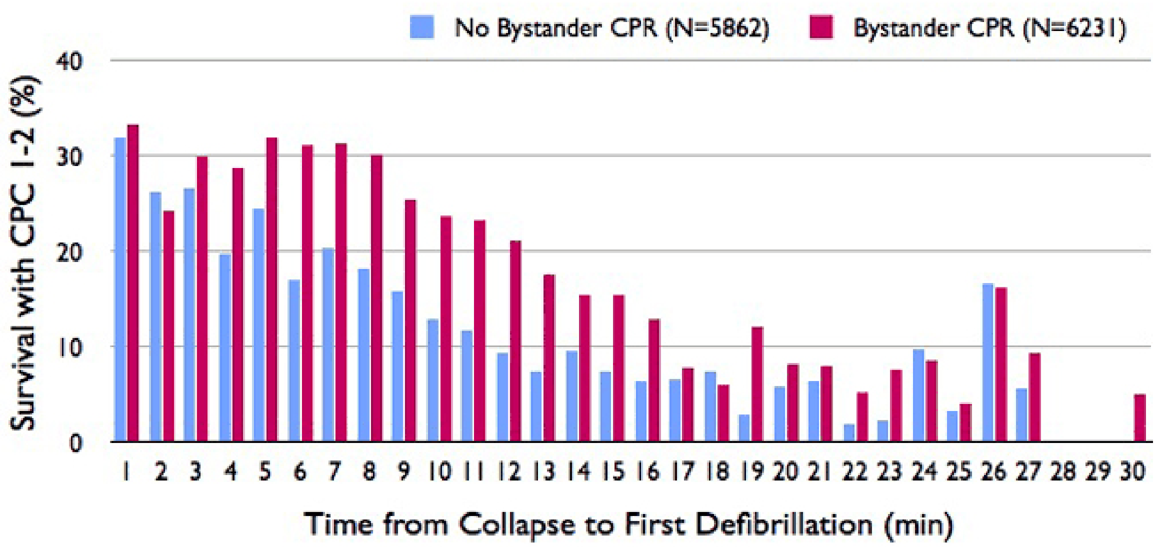
The so-called Chain of Survival has been adopted by the American Heart Association and the International Liaison Committee on Resuscitation (ILCOR) in 1992 and 1997, respectively. It has been credited with improved survival following OHCA in a number of publications (Boyce *et al.*, 2015; Stromsoe *et al.*, 2015). As discussed in Section 1.1, irreversible cellular damage and ultimately death occurs within minutes of untreated cardiac arrest. The Chain of Survival emphasises that, for resuscitation efforts to be successful, a number of interventions need to be linked up and delivered in a timely fashion by bystander, EMS systems and receiving hospitals.

The first link concerns the early recognition and call for help from the public. In a recent publication, approximately 50% of patients who suffered OHCA had warning symptoms, such as chest pain and dyspnoea, prior to the OHCA. For only 19% of these patients, EMS assistance was requested for these symptoms (Marijon *et al.*, 2016). The survival rate for patients where EMS was called prior to OHCA was 32.1%, compared to 6.0% for those where EMS was only activated once OHCA had occurred.

The next link in the Chain of Survival is early CPR, most frequently commenced by bystanders and then continued by EMS providers. The importance of immediate bystander CPR for survival following OHCA cannot be overstated (Sasson *et al.*, 2010) and community teaching programmes and EMS dispatcher instructions are common initiatives to improve bystander CPR rates (Beard *et al.*, 2015; Malta Hansen *et al.*, 2015). Bystander or EMS provider CPR buys time by creating a degree of blood flow to vital organs during OHCA (Genbrugge *et al.*, 2015). However, CPR alone generally cannot reverse OHCA without specific therapies aimed at the underlying cause of the OHCA, such as defibrillation, the third link of the Chain of Survival (Soar *et al.*, 2015).

Early defibrillation has traditionally relied on optimised EMS response times but there is increasing interest in community responders or members of the public using automated external defibrillators (AEDs) (Kitamura *et al.*, 2016; Hansen *et al.*, 2015). Figure 1.8 demonstrates the time-sensitive effect of combined bystander CPR and early defibrillation (Nonogi *et al.*, 2010).

Figure 1.8 Nonogi *et al.* (2010): *Effect of early defibrillation and bystander CPR on survival after witnessed OHCA due to ventricular fibrillation*, with permission from Circulation (license number 4093080631511)



CPR: Cardiopulmonary resuscitation, CPC: Cerebral Performance Category

Finally, optimised post-resuscitation care spans EMS care, emergency departments, intensive care, cardiology wards and outpatient rehabilitation. It is crucial not only for survival but also for quality of life after OHCA (Andrew *et al.*, 2017). Achieving meaningful survival after OHCA is a complex, long and potentially expensive healthcare process (Elmer *et al.*, 2016).

However, a key message of the Chain of Survival is that simple interventions (CPR and defibrillation), delivered early, have the biggest impact on patients' chances of survival (Resuscitation Council (UK), 2015). Interventions further along the OHCA treatment pathways are increasingly complex and less evidence-based. More importantly, for a patient to benefit from later interventions such as PCI or intensive care, they need to have survived to this stage, which depends heavily on early CPR and defibrillation. On the other hand, successful resuscitation resulting in ROSC and survival to hospital admission is only beneficial to an individual patient if the post-resuscitation care that follows results in survival to hospital discharge with an acceptable quality of life. Thus, the concept that every chain is only as strong as its weakest link holds true for the Chain of Survival.

Predictors of survival for individual patients and measurements of successful resuscitation are discussed further in the next section.

1.3 Outcomes from out-of-hospital cardiac arrest

I have demonstrated in Section 1.1 that OHCA is a relatively common event. While certain risk factors exist, it is nearly impossible to predict the time or place that an individual will suffer an OHCA. Section 1.2 gives an overview of the response by EMS (ambulance) services and the interventions delivered by prehospital providers for OHCA. The following section will address two questions: how do we measure successful resuscitation from OHCA and what are the predictors of survival?

1.3.1 Measurement of successful resuscitation outcomes

Section 1.2 describes the response of modern EMS systems to confirmed or suspected OHCA, namely the timely arrival of BLS- or ALS-trained clinicians at scene. I demonstrated that the evidence clearly supports early CPR and defibrillation, but is unclear in regards to many other aspects of EMS care for OHCA.

So how is the quality of prehospital care for OHCA measured? The four commonly used measurements of successful resuscitation are: ROSC at any time during the initial resuscitation; arrival of the patient at hospital with a palpable pulse (survival to hospital arrival); survival to hospital discharge; neurological status at pre-defined time intervals (e.g. at discharge, 3- or 6-months post-discharge). All of these outcome measurements can be described in terms of their relevance to EMS care, patient-focus and how easy they are to obtain.

Achieving ROSC is the first priority of prehospital care for OHCA (Brown *et al.*, 2016). Occurrence of ROSC is usually recorded in EMS records and as a binary outcome it is easily measurable. It is also clearly a consequence of EMS interventions and as such could be used to measure the quality of EMS care. However, not infrequently, ROSC is only a temporary phenomenon that is poorly related to more patient-focused outcomes. Fischer *et al.* (2011) compare different European EMS systems and describe ROSC rates of 21% to 36%. Of these patients with ROSC, rates of re-arrest followed by prehospital death ranged widely (2%, 11%, 36% and 64%) in different EMS systems, severely limiting the value of ROSC as a marker of successful resuscitation after OHCA.

The measurement of survival to hospital arrival requires EMS providers not only to restore spontaneous circulation after OHCA, but also to maintain it until hand-over of care to the in-hospital team (Perkins *et al.*, 2015a). This outcome is measured at the end of the prehospital care phase, making it more relevant than ROSC at any time, while being equally easy to measure. Critics of this outcome measure have pointed out that it is not patient-focused and prehospital interventions can increase rates of survival to hospital arrival, without increasing rates of survival to hospital discharge (Jacobs *et al.*, 2011). Despite this limitation, survival to hospital arrival is a frequently reported outcome in prehospital OHCA studies and is included in the national UK Ambulance Quality Indicator dataset (Association of Ambulance Chief Executives, 2017; Bottiger *et al.*, 2016; Benoit *et al.*, 2015).

Also included in the UK Ambulance Quality Indicator dataset is the possibly most frequently used outcome measure in prehospital OHCA studies, survival to hospital discharge (Association of Ambulance Chief Executives, 2017; Bottiger *et al.*, 2016; Benoit *et al.*, 2015). It combines availability from routine healthcare records with improved patient focus and is easily understood by non-experts, including lay people. The drawbacks are that patients who survive OHCA often spend weeks in hospital while the prehospital care phase is generally measured in minutes. Survival to hospital discharge is therefore a measurement not exclusively of prehospital care but also includes hospital care, particularly when comparing EMS systems in different regions (von Vopelius-Feldt and Benger, 2016a). The other concern is survival of patients with poor neurological function (Yasunaga *et al.*, 2010), which, in the worst circumstances, could be seen as an outcome worse than death (Williams, 1989), or death occurring shortly after discharge from hospital. It is reassuring that more recent studies demonstrate a good quality of life for the majority of survivors of OHCA and a length of life approaching that of the standard population (Andrew *et al.*, 2017; Lindner *et al.*, 2014; Stiell *et al.*, 2009).

Nevertheless, the ideal outcome measure from a patient perspective would be quality of life. Larger trials of OHCA interventions are now tending to use quality of life outcome measures but there is little consistency in regards to when this is measured and what tools are used (Perkins *et al.*, 2016a; Taylor *et al.*, 2016). The obvious downside compared to the other outcomes is the requirement to collect additional data. In the case of delayed follow up, not only hospital but also post-discharge interventions might affect the ultimate quality of life recorded, raising the issue of confounding through treatment variations that follow the EMS phase of care (Elmer *et al.*, 2016). There are also concerns that patients with better outcomes are more likely to consent to follow up, which might result in interventions appearing more effective than they truly are (Salzman *et al.*, 2015).

1.3.2 Factors influencing survival after out-of-hospital cardiac arrest

The most recent publication from the Out-of-Hospital Cardiac Arrest Outcomes Registry (OHCAO) contains over 28,000 cases of OHCA in the UK in 2014, with a rate of survival to hospital arrival of 25.8% and a rate of survival to hospital discharge of 7.2% (Hawkes *et al.*, 2017). Understanding the factors that determine survival after OHCA is necessary to guide expectations of patients' relatives, to plan resource allocation and to allow for comparison of the effects of interventions for OHCA (Martinell *et al.*, 2017).

Prognostication of survival generally occurs at three time points: during OHCA; on arrival at hospital; a few days after hospital admission, if applicable (Fukuda *et al.*, 2015; Goto and Maeda, 2013; Kamps *et al.*, 2013). This section will focus on the prognostic factors relevant to prehospital care, in OHCA of presumed cardiac aetiology. See Figure 1.9 for an overview of prognostic factors identified in the meta-analysis by Sasson *et al.* (2010).

Figure 1.9 Factors influencing survival after OHCA (Sasson *et al.*, 2010), with permission from Circulation (license number 4120141313291)

Variable	Pooled Percentage of Cardiac Arrests With Attribute	Low Baseline Survival		High Baseline Survival	
		Pooled Survival Rate, %	NNT	Pooled Survival Rate, %	NNT
Witnessed by bystander	53% (45.0–59.9)	6.4 (3.5–9.3)	17	13.5 (5.6–21.5)	71
Witnessed by EMS	10% (8.0–11.3)	4.9 (1.3–8.4)	23	18.2 (3.7–32.8)	16
Not witnessed	36% (30.4–40.8)	0.5 (0.2–0.9)		12.1 (7.5–16.7)	
Bystander CPR	32% (26.7–37.8)	3.9 (1.8–6.0)	36	16.1 (11.5–20.7)	24
No bystander CPR	68% (62.6–74.8)	1.1 (0.5–1.8)		12.0 (10.0–14.0)	
Ventricular fibrillation/tachycardia	40% (36.6–43.3)	14.8 (9.4–20.2)		23.0 (13.8–32.2)	
No ventricular fibrillation/tachycardia	60% (56.2–62.9)	0.4 (0.2–0.6)		7.4 (6.1–8.7)	
Asystole	42% (36.0–46.8)	0.2 (0–0.3)		4.7 (1.0–8.4)	
No asystole	58% (52.9–63.8)	4.4 (2.1–6.6)		30.1 (23.8–36.4)	
Return of spontaneous circulation	22% (17.7–25.5)	15.5 (0.0–33.3)		33.6 (24.9–42.2)	
No return of spontaneous circulation	78% (74.5–82.3)	0.1 (0.0–0.2)		1.8 (1.5–2.1)	

NNT indicates number needed to treat to save 1 life.

NNT: Number needed to treat, EMS: Emergency Medical Services, CPR: Cardiopulmonary resuscitation

Prognostic factors can be divided into patient factors (presenting cardiac rhythm; witnessed OHCA; age of patient; location of OHCA) and EMS factors (bystander CPR; EMS response time;

time to defibrillation). While patient factors are generally fixed, much effort is being made to improve EMS factors.

The single most significant determinant of survival in most studies is the presence of a shockable rhythm (see Section 1.1.5) at initial evaluation by EMS providers (von Vopelius-Feldt, Coulter and Benger, 2015; Goto and Maeda, 2013; Sasson *et al.*, 2010). VF or pulseless ventricular tachycardia (VT) can be restored to an organised cardiac rhythm with ROSC, whereas PEA or asystole are frequently due to irreversible anatomical or physiological injury and carry a much worse prognosis (Andrew *et al.*, 2017).

OHCA is witnessed by either EMS providers or bystanders in just over 50% of cases in the UK (Hawkes *et al.*, 2017). Compared to unwitnessed cardiac arrests, bystanders can provide CPR and activate EMS care immediately, resulting in significantly higher survival from witnessed OHCAs (Sasson *et al.*, 2010).

Advancing age is associated with decreasing rates of survival after OHCA in most studies (Martinell *et al.*, 2017; Wissenberg *et al.*, 2015). It is not clear if this is a directly causative effect or if higher age is associated with factors such as co-morbidities and functional status, which in turn influence survival rates (van de Glind *et al.*, 2013)

Similarly, the location of the OHCA is associated with survival, which is lower in OHCA in residential settings, compared to public areas (Chen *et al.*, 2015). However, once other factors, such as shockable rhythm and bystander CPR, have been controlled for the association between location of OHCA and survival is, at least, diminished (von Vopelius-Feldt, Coulter and Benger, 2015; Goh *et al.*, 2013).

The first EMS factor, EMS response time, shows a consistent and clinically significant association between shorter time intervals and higher survival rates after OHCA (Hawkes *et al.*, 2017; Rajan *et al.*, 2016; O'Keeffe *et al.*, 2011). This is probably due to the early provision of CPR and, if applicable, defibrillation, the importance of which was outlined in the concept of the Chain of Survival in Section 1.2.4 (Hawkes *et al.*, 2017). The importance of early EMS provider attendance is further supported by cases where EMS was activated for symptoms such as chest pain or dyspnoea and the patient then suffered an OHCA in the presence of EMS providers. These patients with EMS-witnessed OHCAs have survival rates up to sevenfold higher than those where EMS was activated after the OHCA occurred (Nehme *et al.*, 2015a; O'Keeffe *et al.*, 2011). In contrast, a longer time from OHCA to defibrillation and increasing length of resuscitation are associated with lower chances of survival (Reynolds *et al.*, 2016; Hansen *et al.*, 2015). Given the difficulties of predicting the occurrence of OHCA in an individual patient and the cost of decreasing EMS response times through increased resource provision, much interest has been generated in using the public or first aiders with basic training to provide the two key interventions for OHCA: CPR and defibrillation.

Bystander CPR is frequently quoted to double chances of survival in OHCA; see Figures 1.8 and 1.9. With average (median) EMS response times for OHCA in the UK of approximately 6min (von Vopelius-Feldt, Coulter and Benger, 2015), bystander CPR can delay the deterioration from an initial shockable rhythm to PEA or asystole and bridge the time from OHCA to EMS arrival and professional resuscitation (Hawkes *et al.*, 2017). Many initiatives to improve survival after OHCA therefore include community programmes to increase the rates of bystander CPR, which have been reported to range from 33% to 76% (Boyce *et al.*, 2015; Malta Hansen *et al.*, 2015; McNally *et al.*, 2011).

With advances in technology and reducing costs, public automated external defibrillators (AEDs) are increasingly available and their use is associated with significantly improved survival rates (Kitamura *et al.*, 2016; Boyce *et al.*, 2015).

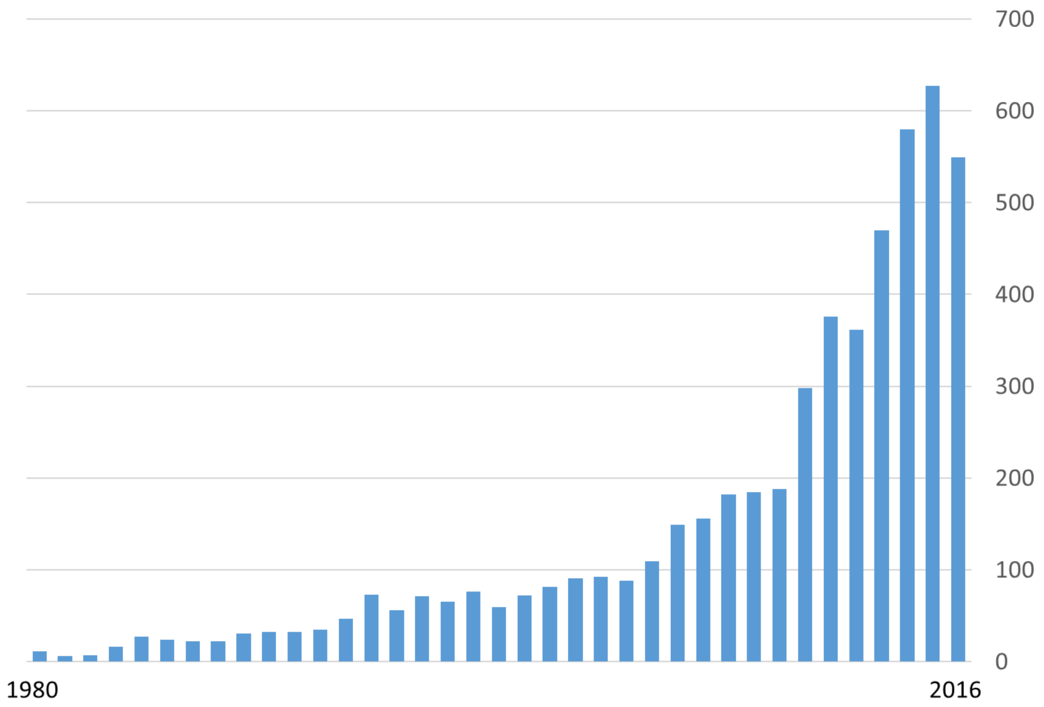
In addition to the patient and EMS factors listed above, research is investigating associations between survival after OHCA and population density (Buick *et al.*, 2015), time of the event (Bagai *et al.*, 2013), co-morbidities (Soholm *et al.*, 2015), patient gender (Bougouin *et al.*, 2015), socio-economic factors (Wells *et al.*, 2016) and race (Moon *et al.*, 2014), amongst others. However, most of these effects are either statistically insignificant once adjusted (Soholm *et al.*, 2015) or of small magnitude (Bougouin *et al.*, 2015), and it remains frequently unclear if they are causative or simply associated with other prognostic factors (Wells *et al.*, 2016; Moon *et al.*, 2014).

This section has demonstrated that survival following OHCA is not only dependent on medical interventions, but is largely influenced by patient factors. Furthermore, what actually constitutes a successful outcome depends on perspective. These are important considerations when comparing findings from different populations or between studies. Furthermore, much of what we know about OHCA stems from observational research, describing associations rather than causation. In the next section, I will discuss the challenges of researching OHCA as well as important efforts to standardise the reporting of results.

1.4 Research in out-of-hospital cardiac arrest

Research in OHCA has seen a steady increase over the last decades, particularly the last 10 years. A search for *"out-of-hospital cardiac arrest"* in PubMed on 19th September 2016 showed an increase from 11 results in 1980 to 549 in 2016; see Figure 1.10 for a yearly breakdown.

Figure 1.10 Number of search results for *"out-of-hospital cardiac arrest"* in PubMed, by year (undertaken on 19th September 2016)



This increase in research is encouraging and seems appropriate, given that coronary artery disease is the most common cause of death worldwide (Finegold, Asaria and Francis, 2013), and OHCA is the first presentation of coronary artery disease in an estimated 40-60% of OHCA cases (de Vreede-Swagemakers *et al.*, 1997; Kannel and McGee, 1985). However, comparing the amount of published research on OHCA to that on other conditions still reveals a stark contrast. A similar basic PubMed search for "*breast cancer*" (19th September 2017) reveals 2,149 and 16,920 search results in 1980 and 2016, respectively. The reasons for this discrepancy is likely multifactorial and beyond the remit of this thesis. One factor that is relevant, however, is that much research in OHCA has to be undertaken outside of the hospital, which imposes important barriers and challenges.

1.4.1 Challenges of prehospital and cardiac arrest research

The challenges of prehospital research, when compared to research in hospital or out-patient clinic settings, are manifold. Firstly, there is geography. Clinical care is delivered by EMS systems which often cover vast areas with varying terrain, climate and population characteristics (Symons and Shuster, 2004). As prehospital care is largely provided in patients' homes, public places or the inside of a moving ambulance, the capture and collection of research data are challenging (McClelland *et al.*, 2015). Add to this the time pressures of emergency care and the general unpredictability of medical emergencies and it becomes clear why setting up high-quality research studies is challenging. A systematic review of prehospital research in 1999 identified a total of 41 randomised controlled trials, of which only four had a sample size of over 1,000 (Brazier *et al.*, 1999). Other authors note a general lack of volume, quality and funding of emergency and prehospital medicine research (Bounes *et al.*, 2013). Nevertheless, factors such as improved paramedic education, information technology to disseminate and collect information and a general enthusiasm by prehospital providers (McClelland *et al.*, 2015; Hargreaves, Goodacre and Mortimer, 2014) have helped important prehospital studies to be completed successfully (Austin *et al.*, 2010; Van't Hof *et al.*, 2008).

Research focusing on OHCA adds its own challenges, with Herlitz *et al.* (2007, p.213) remarking that "*cardiac arrest is one of the most chaotic events in medicine"*. Life-saving diagnostics and treatments need to be delivered in timeframes measured in seconds and minutes, limiting opportunities for data capture, randomisation procedures or adding yet unproven interventions into the complex resuscitation process (Perkins *et al.*, 2015c). The major obstacle to interventional trial designs is that patients in OHCA, by the very nature of the condition, are unable to consent to participation in research (Coats and Goodacre, 2009). Many countries, including the US, Australia and the UK have implemented legal and ethical frameworks that allow patients to be enrolled in research without consent, under strict conditions (van Belle *et al.*, 2015). In the UK, a number of ethical, legal and professional stipulations need to be followed (World Medical Association, 2013; General Medical Council, 2013; Department of Health, 2006). Davies *et al.* (2014) published a framework of questions and considerations that address the relevant requirements when considering emergency research without consent; see Box 1.2.

Box 1.2 Questions and considerations for research where waiver of consent is considered (Davies *et al.*, 2014)

- Is this research needed?
- Is there uncertainty about treatment?
- Is there a need to recruit subjects who lack capacity?
- In the context of the research, is consent or consultation feasible?
- Does treatment need to be given quickly?
- Might delay change the effect of treatment or the results?
- Will procedures accommodate variations in capacity?
- Would the legal representative/consultee be likely to have capacity?
- Is it practical to consult a professional legal representative unconnected to the research?
- What should the patient or legal representative be asked later?

The alignment of ethics, law and professional guidelines, with support from research organisations (Nolan *et al.*, 2015a), has enabled large randomised trials of interventions in OHCA in the UK (Taylor *et al.*, 2016; Perkins *et al.*, 2015c). However, academics, the public and prehospital providers continue to show concern about the ethical appropriateness of randomised research in OHCA (Hargreaves, Goodacre and Mortimer, 2014; Smith, 2014).

Another challenge in OHCA research is the fact that the outcomes of survival to hospital discharge or good neurological outcome (see Section 1.3.1) are relatively rare and, as described in Section 1.3.2, heavily influenced by variations in patient factors. Furthermore, even small changes in OHCA survival rates are clinically important, given the significance of the alternative outcome of death (Nichol *et al.*, 2016). This means that the sample size required for the detection of clinically significant differences in outcome is often in the range of 5,000 to 10,000 patients, which requires significant logistical and funding support for OHCA prehospital research projects (Taylor *et al.*, 2016).

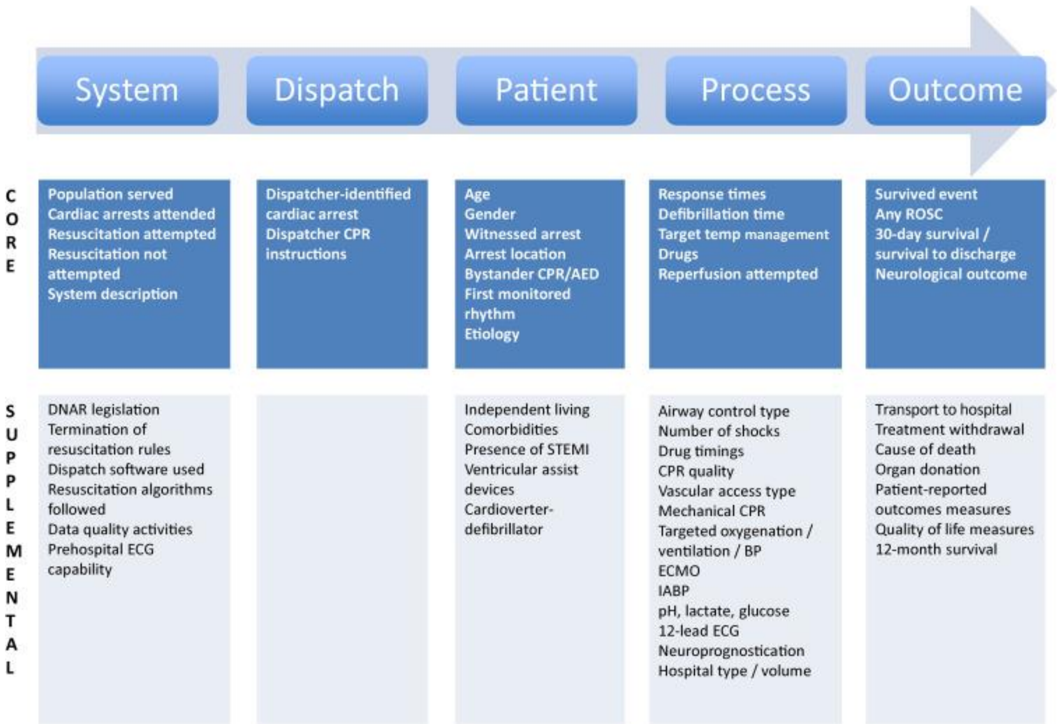
1.4.2 Out-of-hospital cardiac arrest registries and observational research

Given the challenges of conducting research without informed consent and the need for large sample sizes in OHCA research, it is not surprising that many countries have set up national OHCA registries (Goldberger and Nichol, 2013). These registries allow monitoring of epidemiologic data, including trends over time or regional variation in outcomes (Daya *et al.*, 2015; Nehme *et al.*, 2015b; Wang *et al.*, 2015). Commonly, researchers have used the available data in prospective or retrospective observational studies, examining new interventions or changes in practice (Choi *et al.*, 2016; Schober *et al.*, 2016; Vyas *et al.*, 2015).

In the UK, the University of Warwick hosts the OHCAO Registry, which collects data from participating NHS ambulance trusts; see Chapter 7 for more information (Perkins and Brace-McDonnell, 2015).

A major issue for observational research in OHCA is the fact that outcomes are determined by a number of factors other than the variable of interest (see Section 1.3.2), introducing the risk of confounding and bias (Fouche and Jennings, 2016; Lu, 2009). In an effort to improve reporting of confounding variables and the comparison of different treatments or systems for OHCA, a consensus-based guideline, the Utstein template, was published in 1991 (Cummins, 1991). The Utstein template has since been updated twice, reflecting advances in technology and understanding of OHCA, and has been adopted by most OHCA registries (Perkins *et al.*, 2015a). The template includes mandatory core variables as well as supplemental variables relating to the key epidemiological factors (Section 1.1), interventions (Section 1.2), prognostic factors and outcomes (Section 1.3) discussed previously (Perkins *et al.*, 2015a). See Figure 1.11 for a summary of the core and supplemental variables in the Utstein 2014 template.

Figure 1.11 Variables in the Utstein 2014 template (Perkins *et al.*, 2015a), with permission from Resuscitation (license number 4134100961000)



CPR: Cardiopulmonary resuscitation, AED: Automated external defibrillator, ROSC: Return of spontaneous circulation, DNAR: Do Not Attempt Resuscitation, ECG: Electrocardiogram, STEMI: ST-elevation myocardial infarction, BP: Blood pressure, ECMO: Extracorporeal membrane oxygenation, IABP: Intra-arterial blood pressure

Knowledge of the Utstein variables allows comparison between individual study results and between different groups within observational studies. If variables are not equally distributed within a study, statistical methods such as multiple logistic regression or propensity score matching (see Chapter 7) can be used to adjust outcomes, eliminating or at least reducing confounding and bias (Hasegawa *et al.*, 2015; Do Shin *et al.*, 2012).

Another method of comparing the effects of interventions or different EMS systems, suggested by the Utstein group, is to compare survival only for the subgroup of patients with witnessed OHCA and ventricular fibrillation (VF) as the presenting rhythm (Perkins *et al.*, 2015a). This approach has been criticized, as it results in reporting high survival rates (due to the underlying favourable prognostic factors), which are at odds with the general poor survival rates from resuscitation of unselected cases of OHCA (Timmermans, 1999). On the other hand, the argument for reporting the outcomes in this subgroup of witnessed VF OHCA is twofold. Firstly, the generally higher survival rate means that any beneficial effect from a studied intervention is likely to be more pronounced in this group (Lindner *et al.*, 2011). Secondly, the OHCA subgroups of witnessed VF are relatively homogenous in regards to many of the patient or EMS factors discussed in Section 1.3.2 which influence survival (Perkins *et al.*, 2015a). While the results are certainly not generalizable to all cases of OHCA, the internal validity of the study of OHCA interventions improves when analysing only cases of witnessed VF OHCA (Lu, 2009).

1.5 The concept of prehospital critical care

BLS and ALS are the two established international standards of care for OHCA (see Section 1.2.2), with little evidence to suggest benefits of ALS over BLS (Sanghavi *et al.*, 2015; Stiell *et al.*, 2004). A number of EMS systems have established a further level of care, delivered by prehospital critical care providers, however evidence to support this practice is lacking (von Vopelius-Feldt, Wood and Benger, 2014). This section will discuss the origins of prehospital critical care teams and describe their work in more detail. Finally, I will discuss the current evidence base for prehospital critical care.

1.5.1 The evolution of prehospital care

"He went to him and bandaged his wounds, pouring on oil and wine. Then he put the man on his own donkey, took him to an inn and took care of him." (Luke 10:34). The account of The

Good Samaritan in the New Testament, while far predating the development of modern medicine, already contains the fundamental principles of prehospital care: medical treatment at the scene of injury followed by transport to a facility for further care. The roots of modern EMS care are generally traced back to the Ambulances Volantes used by Napoleon Bonaparte's chief physician for the evacuation of wounded soldiers from the battle field in the late 18th century (Sefrin, 2004). Importantly, this first EMS system was not equipped or designed to deliver any medical intervention; the sole purpose was transport from the scene of injury (Sefrin, 2004).

The first example of an organised civilian EMS system was the introduction of a transport carriage for cholera patients in London in 1832 (Chadwick and Smith, 1850). In the UK, this was followed by the foundation of the St. John Ambulance Brigade in 1887, which used uniformed volunteers to provide first aid and transport to hospital at public events (St. John Ambulance, 2012). Similar systems developed across the UK, spreading from the bigger cities along expanding railway lines and other industrial sites, with increasing capacity especially during the second world war (Black and Davies, 2005). While each developing EMS system had slightly different structures and aims, they all continued to focus on transporting the patient to medical care at the nearest hospital as quickly as possible, with very little treatment on scene or en-route (Black and Davies, 2005).

This understanding of EMS as primarily transport systems remained unchanged until the 1960s, when increasing motorisation and the resulting numbers of casualties from road traffic collisions in the UK prompted a critical review of ambulance systems, known as *The Millar Report* (Ministry of Health, 1966). It recommended that ambulance technicians should receive thorough and intensive training in first aid, should be familiar with aspects of the care of medical and surgical patients and also should receive training in a range of non-clinical skills such as communication and driving (Ministry of Health, 1966). This introduction of at least limited clinical care, in addition to transport to hospital, was implemented regionally and variably by the individual ambulance services.

Advances in medical care and technology, as well as concerns about the range of quality of prehospital care in England, led to a further review in the 1980s with the establishment of a national paramedic curriculum with defined clinical and non-clinical competencies (National Health Service Training Division, 1991). The introduction of the paramedic profession shifted the focus of EMS systems from primary transport systems to systems that deliver clinical skills and knowledge to the scene of illness or injury, followed by transport to hospital (Roberts, Allison and Porter, 2003). A significant proportion of paramedics are now based on rapid response vehicles (RRVs) which can reach patients quickly but do not have traditional transport capabilities (Black and Davies, 2005). This development can also be observed in the prehospital treatment of OHCA. In the past, paramedics would have combined BLS with a scoop and run approach, transporting the majority of patients to hospital while in cardiac arrest (Lockey, 2002; Kellermann, Hackman and Somes, 1993). The common practice today is for paramedics to provide ALS at the scene of OHCA, until the patient has either a return of spontaneous circulation or resuscitation is stopped due to futility (Brown *et al.*, 2016).

The trend of providing more care at scene is continuing in the UK. Acute medical care is under strain from an increasing number of patients, with increasingly complex health problems, many of which fall more into the remit of urgent, primary or social care, rather than of traditional emergency care (Department of Health, 2005). Ambulance services are increasingly trying to provide levels of care at scene that avoid the need for transport to hospital altogether (Association of Ambulance Chief Exectutives, 2011). EMS providers are now required to provide increasingly evidence-based care for a wide range of conditions, ranging from minor illness to major trauma (Association of Ambulance Chief Executives, 2017).

This demand has created interest in EMS providers with specialised skills. Paramedics can now undergo additional training to become emergency care practitioners (ECPs) or paramedic practitioners, specialising in urgent care presentations (Mason *et al.*, 2006). General practitioners (GPs) are increasingly embedded in ambulance services to help avoid hospital admission (Association of Ambulance Chief Exectutives, 2011). At the other end of the spectrum of severity, specialist paramedics and doctors provide prehospital critical care to patients with severe illness or injury (von Vopelius-Feldt and Benger, 2013). A need for the specialised skillsets of prehospital critical care providers in the UK has been highlighted in a number of reports over the last years, particularly in the context of major trauma (Findlay, Martin and Smith, 2007; The Royal College of Surgeons of England and the British Orthopaedic Association, 2000).

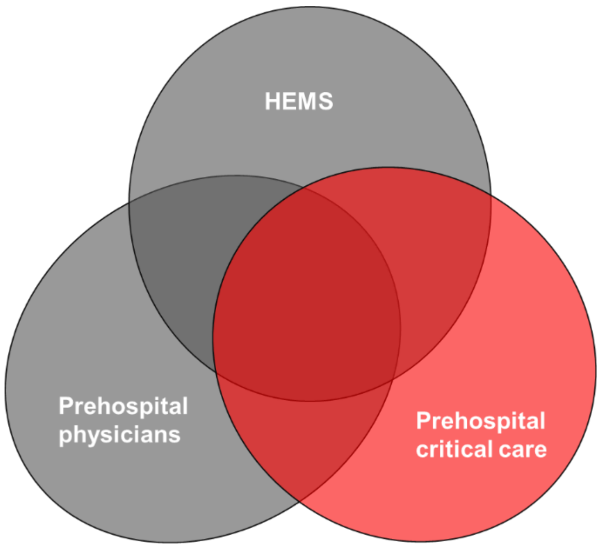
1.5.2 What is prehospital critical care?

"By 'prehospital critical care' we mean the application of the clinical knowledge and skills required for the management of severely ill or injured patients and the requirement for the provision of physiological monitoring and organ or system support … " (Mackenzie *et al.*, 2009, p.367). This definition of prehospital critical care was generally agreed on in the study of EMS stakeholders in the UK. It entails a sensible combination of clinical competencies, specialised medical equipment and a focus on patients with life-threatening emergencies

(Mackenzie *et al.*, 2009). However, it also has significant shortcomings which lead to controversy in practice and research. The skills and knowledge are not clearly defined, and which of them are considered standard or critical prehospital care will vary between EMS systems (Gryniuk, 2001). For example, the provision of ALS (clinical knowledge and skills) for patients in OHCA (severely ill) with ventilation and Adrenaline administration (organ support) would fit the definition of critical care but, in the UK, would not be classified as prehospital critical care (Brown *et al.*, 2016; Mackenzie *et al.*, 2009). A systematic review of the evidence for critical care paramedics identified this lack of a clear definition as a major barrier to current research (von Vopelius-Feldt, Wood and Benger, 2014). To further complicate matters, prehospital critical care is often seen as synonymous with physician-delivered prehospital care or helicopter-based emergency medical services (HEMS) (Mikkelsen *et al.*, 2015; Butler, Anwar and Willett, 2010; Botker, Bakke and Christensen, 2009).

My previous work has looked at this issue in detail and I created a competence-based definition of prehospital critical care, which also has consequences for the configuration, transportation, dispatch and clinical governance of prehospital critical care services (von Vopelius-Feldt and Benger, 2014a). The first thing to note is that prehospital critical care is not synonymous with physician-delivered prehospital care or HEMS (Jashapar, 2011). However, it is equally important to note that significant overlap exist between these three aspects of prehospital care; see Figure 1.12 (von Vopelius-Feldt, Coulter and Benger, 2015; von Vopelius-Feldt and Benger, 2013).

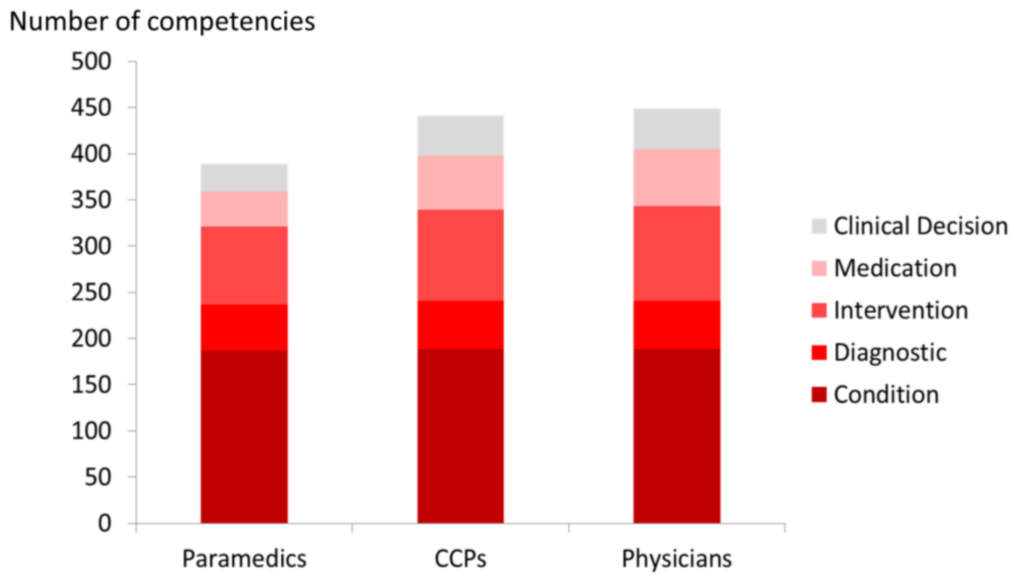
Figure 1.12 Venn diagram of prehospital critical care, physician-delivered prehospital care and Helicopter Emergency Medical Services



HEMS = Helicopter Emergency Medical Services

In order to create a competence-based definition of prehospital critical care, I analysed the clinical competencies of UK ALS paramedics, critical care paramedics and prehospital critical care physicians through triangulation of data from protocols, guidelines, ambulance equipment, observation of clinical practice and provider interviews; see Figure 1.13 (von Vopelius-Feldt and Benger, 2014a).

Figure 1.13 Clinical competencies of ALS paramedics, critical care paramedics and prehospital critical care physicians (von Vopelius-Feldt and Benger, 2014a)



CCPs: Critical care paramedics

UK ALS paramedics possess approximately 450 clinical competencies, with some regional variation (Brown *et al.*, 2016). My research showed that critical care paramedics and physicians working for the Great Western Air Ambulance (GWAA) have approximately 50 additional competencies, mainly due to an increased number of interventions, medications and clinical decision making skills (von Vopelius-Feldt and Benger, 2014a). These critical care skills can be grouped into four categories: prehospital anaesthesia; procedural sedation; advanced cardiovascular management; surgical interventions. More important than the precise number of these additional critical care competencies is the fact that many of them relate to complex, high-risk treatments for severely ill patients which are, fortunately, required only rarely (von Vopelius-Feldt and Benger, 2014a; Deakin, King and Thompson, 2009). Consequently, critical care providers need to have thorough training, frequent exposure to severely ill patients and robust clinical governance arrangements to ensure that risks to patients are minimised (von Vopelius-Feldt and Benger, 2013; Cushman *et al.*, 2010).

Attempts at simply introducing critical care skills to ALS paramedics without these supporting structures have been shown to result in harm, rather than benefit, to patients (Davis *et al.*, 2003).

Box 1.3 Definition of a prehospital critical care provider (von Vopelius-Feldt and Benger, 2014a)

- Targeted dispatch to only critically ill or injured patients
- Competencies beyond ALS level care, in at least one of the following categories
    - Prehospital anaesthesia
    - Procedural sedation
    - Cardiovascular management
    - Surgical procedures
- Access to a structured training, skill maintenance and governance programme

ALS: Advanced Life Support

In the UK, prehospital critical care teams are increasingly available but not ubiquitous (von Vopelius-Feldt and Benger, 2014b; Hyde *et al.*, 2012). A national survey I undertook in 2013 identified costs of critical care and a lack of evidence as the main reasons that ambulance trusts do not provide prehospital critical care (von Vopelius-Feldt and Benger, 2014b). Another question which was raised in my survey, and also previous research, was if there is actually a clinical need for critical care in the UK, given the level of care already provided by ALS paramedics (von Vopelius-Feldt and Benger, 2014b; Mackenzie *et al.*, 2009).

1.5.3 The evidence for prehospital critical care

Like many aspects of EMS, prehospital critical care has been developed based on a combination of clinical demand, historical factors and common sense, rather than from a solid evidence base (Findlay, Martin and Smith, 2007; Pozner *et al.*, 2004; Sefrin, 2004). The same challenges and limitations described for prehospital research in Section 1.4.1 apply here. While a detailed review of the evidence for prehospital critical care is beyond the remit of this thesis, I will provide a general overview in this section.

In 2014, I undertook a systematic review of paramedic-delivered prehospital critical care (von Vopelius-Feldt, Wood and Benger, 2014). The review included 12 studies, of which one was a randomised controlled trial; all the others were observational studies. All but one publication focused on patients with traumatic injuries, none examined paramedic-delivered prehospital critical care for OHCA. Five publications compared outcomes between paramedic- and physician delivered prehospital critical care. The eight publications which compared paramedic-delivered prehospital critical care with BLS or ALS prehospital care showed mainly better outcomes for critical care paramedics attending patients with severe trauma, but small sample sizes and potential confounding limit confidence in the results (Bernard *et al.*, 2010; Mitchell, Tallon and Sealy, 2007).

The body of literature describing physician-delivered prehospital critical care is similar, in that it focuses largely on trauma and is limited by observational research designs (Botker, Bakke and Christensen, 2009). The review by Botker, Bakke and Christensen (2009, p.1) concluded: "*Our systematic review revealed only few controlled studies of variable quality and strength examining survival with prehospital physician treatment. Increased survival with physician treatment was found in trauma and, based on more limited evidence, cardiac arrest*." Since then Garner *et al.* (2015) have provided the currently most definitive study of the effect of physician-delivered prehospital critical care for severe trauma; a randomised controlled trial of either physician HEMS or ALS paramedic treatment. While there were issues with non-compliance, the study showed no difference in 30-day survival or neurologic recovery (Garner *et al.*, 2015).

In regards to OHCA, Bottiger *et al.* (2016) published a meta-analysis titled *Influence of EMS-physician presence on survival after out-of-hospital cardiopulmonary resuscitation*. The meta-analysis showed a clear association between survival and EMS physician presence. However, these results should be interpreted with caution, as there is evidence of systematic confounding favouring EMS physicians, selective interpretation of results and non-addressed heterogeneity (von Vopelius-Feldt, 2017; von Vopelius-Feldt and Benger, 2016). A significant limitation, which most of the above publications share, is that they focus on comparisons between either HEMS systems and ground EMS systems or physicians and paramedics, requiring a certain degree of extrapolation when examining the potential benefits of prehospital critical care itself.

1.5.4 Costs of prehospital critical care

Given the lack of clear evidence for benefits from prehospital critical care, the concerns raised regarding the potential costs need to be taken seriously (von Vopelius-Feldt and Benger, 2014b). As outlined in Figure 1.12, prehospital critical care can be provided in a number of configurations, with important cost consequences. Common configurations in the UK are

- HEMS critical care team, paramedic and/or physician delivered. One team covers a large geographical area and population (von Vopelius-Feldt and Benger, 2013).
- Ground-based prehospital critical care team, paramedic and/or physician delivered. Often based in densely populated urban areas, covering a smaller geographical area but significant population (Younger, 2015).
- Decentralised ground-based critical care providers. Mainly delivered by a larger number of individual critical care paramedics distributed strategically over a large geographical area (Jashapar, 2011).

To make matters more complex, most centralised prehospital critical care models in the UK (particularly if HEMS-based) are financed in large parts through local/regional charities (Association of Air Ambulances, 2017). A common financial model is for the costs of helicopters, rapid response vehicles (RRVs) and specialised equipment to be provided by a charity, while paramedic salaries and standard medical equipment are financed by an NHS ambulance service (Association of Air Ambulances, 2017). Prehospital physicians have traditionally volunteered their prehospital care services (Hyde *et al.*, 2012). However, there is a move towards salaried prehospital physicians with the inception of a nationally recognised subspecialty of prehospital emergency medicine (Intercollegiate Board for Training in Pre-hospital Emergency Medicine, 2012).

To my knowledge, no scientific research has attempted to untangle and describe the costs of prehospital critical care in these complex settings. However, a number of cost-analyses focus on HEMS systems, which can provide some idea of the costs of a HEMS-based prehospital critical care service. Snooks *et al.* (1996) reviewed HEMS systems in Sussex, Cornwall and London and found them to cost £55,000, £600,000 and £1,200,000 per annum, respectively. They concluded that HEMS systems are "*costly, the health benefits are small, and there are limited circumstances in which the pre-hospital performance of an ambulance service in England and Wales can be improved [by HEMS]"* (Snooks *et al.*, 1996, p.67). It should be noted that neither Sussex nor Cornwall HEMS would have provided prehospital critical care at the time of the study. A more recent systematic review of economic analyses of HEMS systems noted large variations in costs and benefits, but also the need to consider variations in factors such as health care systems, the surrounding EMS systems and geography. It recommended that any future economic analysis should be "*tailored to account for local system factors"* (Taylor *et al.*, 2010, p.10). Delgado *et al.* (2013) used a decision-analytic model for HEMS associated costs and benefits in the US. They calculated that, at a threshold of $50,000 per quality-adjusted life year (QALY), HEMS systems needed to save 3.3 lives per 100 patients to be cost-effective. The authors conclude that HEMS systems should therefore focus on severely ill patients, rather than minor or moderate injury or illness (Delgado *et al.*, 2013).

This section has described prehospital critical care as an emerging concept in increasingly professional and specialised EMS systems. I have provided a description of prehospital critical care which can guide interpretation and development of research in the field. Despite a lack of clear scientific evidence, prehospital critical care is increasingly but variably implemented in the UK, at significant cost.

1.6 Prehospital critical care for out-of-hospital cardiac arrest

With survival rates from OHCA remaining disappointingly low, there is much interest in new therapeutic opportunities (Johnson *et al.*, 2014). In modern EMS systems, BLS has been superseded or supplemented by ALS. It would seem intuitive that raising the level of care further, to prehospital critical care, might improve survival rates following OHCA. However, Section 1.5.3 summarised the lack of clear evidence to support this hypothesis. It is therefore worth considering the mechanisms by which prehospital critical care teams might improve survival after OHCA. For this purpose, it is worth dividing the resuscitation process into three stages: The cardiac arrest phase; the post-ROSC phase; the phase of hospital treatment.

1.6.1 Prehospital critical care during out-of-hospital cardiac arrest

Treatment during the cardiac arrest phase of OHCA follows the highly standardised ALS algorithms shown in Section 1.2.2. UK paramedics are trained to provide ALS care, raising the question of how critical care teams might provide additional patient benefits during this phase.

The first possibility is the use of therapeutic interventions which are not included in the ALS algorithms. Magnesium Sulphate, Calcium Chloride, Sodium Bicarbonate or fibrinolytic drugs are frequently available to prehospital critical care providers and can be used during OHCA at their discretion (von Vopelius-Feldt and Benger, 2014a). Mechanical CPR devices also fall into this category. Unfortunately, none of these therapeutic interventions has been shown to improve survival from OHCA in unselected OHCA populations; see Figure 1.16 (Jentzer *et al.*, 2016; Bottiger *et al.*, 2008). Advanced surgical interventions for non-traumatic OHCA include thoracostomy to relieve tension pneumothorax and emergency hysterotomy for

OHCA in pregnancy. Both procedures are potentially life-saving, however, the incidence of either condition being present in OHCA is very low (Beun *et al.*, 2015; Rose *et al.*, 2015). Second, advanced diagnostic options, such as the use of ultrasound or a point-of-care blood sample analyser, might allow prehospital critical care providers to treat specific pathology rather than apply the same protocol to all patients (Jentzer *et al.*, 2016; Ahn *et al.*, 2011). However, neither of these two diagnostic technologies have been rigorously assessed in OHCA (Tsou *et al.*, 2017; Truhlar *et al.*, 2015).

Finally, there is evidence that increasing exposure of prehospital providers to OHCA is associated with better survival (Dyson *et al.*, 2016). In this case, potential benefit from prehospital critical care teams might not come from diagnostic or therapeutic options beyond ALS algorithms but from the much more difficult to measure experience in, and quality of, clinical care, independent of the formal level of care delivered.

The counter-argument to prehospital critical care being beneficial during the early cardiac arrest phase of OHCA resuscitation is that prehospital critical care providers frequently aren't present at this time. In my pilot study, ALS paramedics arrived at the scene of an OHCA 6 minutes after the initial call was made, whilst the prehospital critical care team was only dispatched 6 minutes after the initial call and then required an average of another 14 minutes to arrive at scene (von Vopelius-Feldt, Coulter and Benger, 2015). These findings are similar to Lyon and Nelson (2013) who describe a median 31 minutes interval from collapse to HEMS arrival for OHCA. Of patients where resuscitation resulted in ROSC, this was achieved by the ALS ambulance crews prior to prehospital critical care arrival in 50% of cases (Lyon and Nelson, 2013).

While it might be beneficial for a prehospital critical care team to be present at the scene of OHCA as early as possible, there are practical barriers to achieving this. The median response time of 6 minutes for the first EMS resource in my pilot study was achieved through a pre-alert system, in which one or multiple vehicles are mobilised shortly after receiving the 999 call. This model results in a high number of EMS vehicles being stood down, once more clinical information is gathered (Johnson and Sporer, 2010). Dispatching a prehospital critical care team in a similar manner, especially when helicopter-based, would increase costs significantly and would make the prehospital critical care team unavailable for other incidents of critical illness or trauma occurring around the same time (Giannakopoulos *et al.*, 2012).

1.6.2 Prehospital critical care following return of spontaneous circulation

The next stage at which prehospital critical care might improve outcomes from OHCA follows the initial resuscitation phase. While care of the cardiac arrest phase of OHCA follows a clear ALS algorithm, the care of a patient after ROSC is more complex (Soar *et al.*, 2015). Patients are often severely haemodynamically unstable due to arrhythmias and cardiac dysfunction, as well as neurologically impaired, requiring interventions and multi-organ support to prevent recurrence of OHCA (Girotra, Chan and Bradley, 2015).

Many of the interventions required for this optimised prehospital post-resuscitation care fall within the domain of critical care skills described in Section 1.5.2 (von Vopelius-Feldt and Benger, 2014a). These critical care competences can largely be categorised into two groups of advanced haemodynamic management (cardiac ultrasound, cardiac pacing, anti-arrhythmic drugs, inotropes and vasopressors) and prehospital anaesthesia (sedation, paralysis). While no research has been undertaken to address the direct benefits of these interventions following ROSC after OHCA, they are very commonly initiated on arrival of the patient in the emergency department and then continued in the intensive care unit (Nolan *et al.*, 2015b). An important assumption underlying the proposed benefits of prehospital critical care during the prehospital, post-ROSC phase is that hospital-level interventions provided as early as possible (i.e. prehospital) improve outcomes for patients.

1.6.3 Transport to cardiac arrest centres

In Section 1.2.3 I described the current development of regional cardiac arrest centres, which, through a combination of high volumes of OHCA and specialised interventions, have shown improved survival rates following OHCA (OHCA Steering Group, 2017; Elmer *et al.*, 2016). Regionalisation of care for complex conditions has been shown to be beneficial for a variety of complex health conditions, from major trauma to paediatric surgery or specialised cancer services (Metcalfe *et al.*, 2016; Salazar *et al.*, 2016; Colavita *et al.*, 2014).

A regionalised system for OHCA requires EMS providers to transport patients with ROSC over longer distances to the cardiac arrest centre, rather than to the nearest available hospital (OHCA Steering Group, 2017). As discussed in Section 1.5.2, patients with ROSC frequently require complex multi-organ support to prevent prehospital recurrence of the OHCA. Prehospital critical care providers can provide this level of care and facilitate potentially safer transfer to a regionalised cardiac centre, particularly if they also have access to a helicopter for longer distances (von Vopelius-Feldt, Coulter and Benger, 2015). In this case it may actually be the destination hospital, rather than prehospital critical care per se, that is responsible for an improved patient outcome. However, it is worth noting again that there is no clear evidence showing patient benefit from prehospital critical care during any of the three phases of OHCA described in this section.

1.6.4 The belief in prehospital critical care

Throughout Sections 1.5 and 1.6 I have demonstrated the lack of clear evidence underpinning prehospital critical care, particularly in regards to OHCA. Yet, there is a belief in this concept that seems at odds with the lack of evidence supporting it, particularly when compared to the process of evaluating the benefits of other healthcare innovations (Craig *et al.*, 2008). This belief is evidenced by public support through charities, funding through the National Health Service, and EMS providers' daily actions. Is it that, faced with the most recent OHCA survival rates in the UK still below 8% (Hawkes *et al.*, 2017), healthcare providers and the public just need to believe in something that works?

Prehospital critical care teams are extremely unlikely to cause harm to their patient, given that they consist of very experienced and highly trained providers (von Vopelius-Feldt and Benger, 2014a). When comparing prehospital critical care with ALS for OHCA, the scenario is one of either equal or better outcomes, which might satisfy some stakeholders.

Personal accounts of members of the public or prehospital providers might attribute cases of survival to the advanced level of care, whereas death would be attributed to the severity of the underlying condition. This kind of bias generally favours the advanced intervention, in this case prehospital critical care (Shapiro, 2008). In my pilot study, there is clear evidence of confounding in favour of critical care teams (von Vopelius-Feldt, Coulter and Benger, 2015). OHCA survival rates in the ALS and prehospital critical care groups were 6.5% and 15.8%, respectively ($p<0.001$). Only after adjusting for an imbalance in prognostic factors did the possible survival benefit from prehospital critical care team attendance become non-significant (OR 1.54, 95% CI 0.89–2.67).

Like other aspects of EMS provision, prehospital critical care in the UK has been widely implemented prior to scientific evaluation, with some doubting its benefit and others believing in it strongly (Mackenzie *et al.*, 2009). I have shown in Section 1.3.1 and 1.3.2 that the outcome of interest (survival, neurological recovery) is separated from the intervention (prehospital critical care) by weeks of hospital treatment and is also largely determined by patient factors independent of the level of prehospital care. The true effect of prehospital critical care on survival after OHCA is therefore not readily observable in contrast to, for example, the analgesic effect of intravenous Morphine or haemostatic effects of a pressure bandage on a bleeding wound. This lack of observable long-term consequence of prehospital critical care for OHCA creates a vacuum which is largely filled with belief of either benefit or a lack of benefit. In Chapter 3, I will argue that, in order to progress the discussion around prehospital care for OHCA, these beliefs needs to be challenged by scientific evidence, transforming opinions into knowledge.

1.7 Summary

I have shown that OHCA is an important health problem, with survival rates ranging from 5% to 20%, resulting in significant loss of life years globally. OHCA is the common endpoint of a variety of conditions, with coronary artery disease being responsible for the vast majority of events. There are well established risk factors for OHCA, but predicting the time or place of OHCA in an individual patient is impossible. If untreated, irreversible organ damage and death can occur within minutes of OHCA, clinically signified by a deterioration from ventricular fibrillation or pulseless electrical activity to asystole.

Successful treatments have been developed over the last decades, with the main focus on immediate CPR and defibrillation, commenced by bystanders and continued by EMS providers. Modern EMS care for OHCA can be divided into BLS and ALS. The significant survival benefits from timely provision of BLS interventions has been shown consistently in research. ALS, which includes intravenous medication and lung ventilation, has not been proven to improve survival further, when compared to BLS. Neither have a range of therapeutic possibilities (antiarrhythmic drugs, mechanical CPR, thrombolysis) which have been tried over the years.

Outcomes from OHCA resuscitation can be measured at different time-points. Early outcomes are potentially more focused on prehospital treatment but are less patient-focused. The most common measure is survival to hospital discharge. Factors that influence survival are largely patient factors (cardiac rhythm; witnessed OHCA; age) but also EMS factors (EMS response time; bystander CPR).

Research in prehospital care is challenging due to the wide geographical spread of EMS care, time pressure and the inability to gain informed consent from patients in many situations. As survival is relatively rare and influenced by many different factors, large sample sizes are required to detect clinically important differences in survival with adequate power. Therefore, many studies are observational and utilise national OHCA registries. The Utstein template was developed to guide design and reporting of such observational OHCA research. It includes epidemiological, patient and system factors of OHCA, which allows outcomes to be adjusted through statistical methods such as multiple logistic regression or propensity score matching.

Prehospital critical care is a recent development, following a century-long shift of EMS systems' focus from transport to providing increasingly complex medical care at the scene. It can be defined through a combination of provider skills, dispatch and clinical governance. In the UK prehospital critical care teams are widespread but not universal, and there are questions regarding the clinical benefits and costs of providing this level of care. Research seems to support prehospital critical care for major trauma, but less so for OHCA. The costs are potentially significant but depend heavily on the model of prehospital critical care studied. Furthermore, most services in the UK are funded through a mixture of charitable organisations and the National Health Service.

As prehospital critical care is intended to improve the treatment of the most critically ill or injured patients, it seems intuitive for critical care teams to attend OHCA. Potential benefits could occur at three stages of OHCA: the cardiac arrest phase; the post-ROSC phase; treatment at a cardiac centre. Most of the hypotheses for benefits at each of these stages are based on extrapolation of data or common sense, rather than rigorous scientific research. Prehospital critical care is unusual within healthcare in the way it is funded and supported by mixed evidence, common sense and belief.

2. Aims and Objectives

In Chapter 1 I have demonstrated that survival rates following out-of-hospital cardiac arrest (OHCA) remain low, despite significant efforts to improve care. The current standard of care in the United Kingdom (UK) and most modern emergency medical services (EMS) is Advanced Life Support (ALS). In some areas of the UK, prehospital critical care is provided in addition to ALS, but this is inconsistent and frequently funded by charities. Prehospital critical care can be defined as interventions beyond ALS, delivered by a group of specialised prehospital providers. There is little evidence for benefit from prehospital critical care for OHCA, and practice in the UK varies. Unanswered questions are the impact of prehospital critical care on patient outcomes, how exactly it differs from ALS, its costs and even how these questions should be addressed in research.

The aim of this thesis is to provide key stakeholders in prehospital care with the information required to guide the funding and configuration of prehospital critical care for OHCA, within the complex setting of mixed charity and National Health Service (NHS) funding.

2.1 Objective 1

Objective: To search and critically appraise the current literature regarding the impact of prehospital critical care on patient outcomes following OHCA.

Rationale: There are a number of publications which address the research question, but critical appraisal and synthesis of this literature is required to evaluate their validity and generalisability.

Methods: Systematic review of the literature.

2.2. Objective 2

Objective: To estimate the effect of prehospital critical care on survival following OHCA when compared to ALS.

Rationale: Prehospital critical care is a complex intervention of largely unproven benefit in OHCA. Studying its effects on a patient-centred outcomes in the UK setting is required to support funding decisions.

Methods: Prospective, multi-centre observational study of cases of OHCA with the primary outcome of survival to hospital discharge following either ALS or prehospital critical care.

2.3 Objective 3

Objective: To understand what interventions are being delivered by prehospital critical care practitioners during their management of OHCA patients and their potential effects on survival.

Rationale: Prehospital critical care can be seen as a bundle of interventions, which vary significantly in their application between EMS provider organisations but also between individual cases within the same system. Understanding exactly what happens during the care of patients with OHCA and which interventions are associated with improved survival can help inform the optimal configuration of EMS responses to OHCA.

Methods: Prospective, multi-centre observational study recording prehospital critical care interventions used during the management of people with OHCA and their association with survival.

2.4 Objective 4

Objective: To describe the costs of prehospital critical care for OHCA, with reference to the costs of ALS.

Rationale: Prehospital critical care for OHCA patients comes at an increased cost, which is currently shared between NHS and charity funding, and also depends largely on the transport platform used (helicopter or car based).

Methods: Cost analysis of different models of prehospital critical care, from a funder's perspective.

2.5 Objective 5

Objective: To examine stakeholders' views on research and randomisation of prehospital critical care for patients with OHCA.

Rationale: Prehospital critical care exists in a complex environment due to its unique funding structure and uncertainty around it being required or beneficial. Informal discussions with stakeholders during the planning phase of this PhD demonstrated a wide and often opposing range of views as to how prehospital critical care for patients with OHCA should be researched.

Methods: Qualitative interviews and focus group discussions with key stakeholders.

2.6 Presentation of results

Due to the practical aspects of the methods used for each of these objectives, I was not able to address the objectives in the order outlined above. The prospective nature of the data collection for Objectives 2 and 3 meant that the relevant analyses could only be undertaken towards the end of the PhD project. An important aspect of this thesis is to demonstrate my "*capacity to adjust the project design in the light of emergent issues and understandings"* (University of the West of England, 2018). In order to support this doctoral qualification descriptor and to maintain a logical flow throughout the thesis, I have therefore decided to present Chapters 4 to 8 in the chronological order in which the relevant research was undertaken. Given that each objective can be seen as a distinct research project, I will present methods, results and discussion for each research phase separately, before then synthesising and appraising the overall thesis in Chapters 9 and 10. At that point, I hope to be able to answer the following questions:

1. What is the best estimate of the effect of prehospital critical care on survival following OHCA? And what are the best and worst case estimates?
2. Which prehospital critical care interventions are frequently delivered? Which interventions are associated with improved survival?
3. What does prehospital critical care for OHCA cost? What are the opportunity costs?

4. Can stakeholders agree on an ideal way to research this and similar questions in a way that is satisfactory for all stakeholders? Is randomisation of prehospital critical care feasible?

3. The research paradigm

Before embarking on the quest of creating new knowledge about prehospital critical care and out-of-hospital cardiac arrest (OHCA), it is important to discuss the research paradigm which underpins this thesis. According to Kuhn (1962), research paradigms are a set of common beliefs and agreements shared between scientists about how research problems should be understood and addressed. While the origin of Kuhn's (1962) paradigms is rooted in history and philosophy, his definition emphasises the importance of paradigms for communication between scientists (and lay-persons) and for the choice of methods of scientific inquiry in a given research project. A reader of this thesis might consider the methods and interpretation of results to be incoherent or incorrect, if viewed through a different paradigm from the one presented here. By clearly describing the research paradigm, the methods and the results of this thesis can be assessed within the rules and assumptions of that research paradigm.

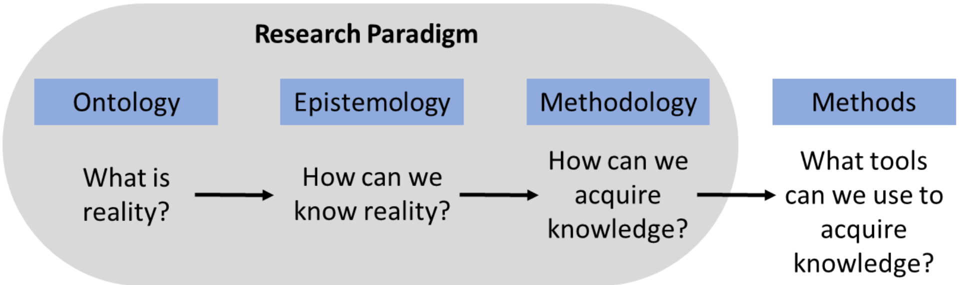
3.1 Ontology, epistemology and methodology

A useful way to approach a research paradigm is to examine its key features in each of the following three domains (Guba, 1990).

- Ontology – What is the nature of reality?
- Epistemology – How do you know something?
- Methodology – How do you go about finding out?

Figure 3.1 gives an overview of how these three domains combine to create a research paradigm and inform the choice of research methods.

Figure 3.1 Graphic representation of the research paradigm domains, adapted from Denzin and Lincoln (2000) and Broom and Willis (2007)



Ontology is frequently explained by the questions it asks (What is a thing? Will I be the same person tomorrow as I am today? Into what categories can we sort existing things?) rather than by the answers it provides to these questions (Wikipedia, 2018). The main aspect of ontology which is relevant to healthcare research is the question of whether a singular reality exists or whether multiple realities are constructed subjectively within given contexts (Leavy, 2014).

Epistemology builds on this by proposing sets of rules and assumptions as to how reality can be understood and known by humans. As Table 3.1 shows, the list of epistemological theories is extensive and a comprehensive review is not within the scope of this thesis.

Finally, methodologies link the worldviews contained in ontology and epistemology to the research methods, by providing a strategy of analysis in keeping with the principles of the chosen paradigm (Darlaston-Jones, 2007).

In the following sections, I will focus on the most relevant and widely adopted research paradigms, contrasting positivism and interpretivism, before describing the paradigm adopted for this research; pragmatism. I will describe the underlying ontology, epistemology and resulting methodology for each paradigm.

Table 3.1 Alphabetical list of epistemological theories, adapted from Wikipedia (2017)

Coherentism	Naturalized epistemology
Constructivist epistemology	Objectivist epistemology
Contextualism	Phenomenalism
Determinism	**Positivism**
Empiricism	Pragmatism
Epistemological idealism	Reductionism
Fallibilism	Reliabilism
Foundationalism	Representative realism
Holism	Rationalism
Infinitism	Skepticism
Innatism	Theory of Forms
Internalism and externalism	Transcendental idealism
Interpretivism	Uniformitarianism
Naïve realism	

3.2 Two views of the world: positivism versus interpretivism

Throughout my medical career and until I undertook my MSc in Health Research at the University of Bath, I held strong positivist ideas without being aware of it. This is probably true for many of my medical colleagues, as positivism has been the underlying principle of traditional research in the natural sciences (Ashcroft, 2004). So what are the features of a positivist paradigm?

It starts with an ontology which assumes that there is a singular and true reality, governed by laws of physics or chemistry. Through testing and measuring with ever increasing accuracy, our understanding and hypotheses of this reality become more and more accurate and most observed phenomena will one day be explained by science (Guba, 1990). The positivist answer to if and how we can know reality is therefore a definite yes, through scientific experiments and testing of hypotheses.

The methodology most closely associated with positivism in healthcare is evidence-based medicine with its emphasis on a hierarchy of evidence and the methods of randomised controlled trials (RCTs) (OCEBM Levels of Evidence Working Group, 2016; Elstein, 2004). Biases are seen as barriers to obtaining truthful measures and much effort should be spent on designing research in a way that minimises bias (Taylor *et al.*, 2016).

Post-positivism can be seen as a slightly less stringent version of positivism, where our knowledge of reality is limited by the imprecision of our scientific instruments and senses, and truth can therefore only be estimated, not known for certain (Denzin and Lincoln, 2000).

More recently, the traditional research paradigms have been challenged by interpretivism. Here, there is no single reality, rather a multitude of socially constructed realities, which differ between individuals and societies (Leavy, 2014). Knowledge about reality is therefore a subjective entity shaped by individuals' experiences, character and social context (Darlaston-Jones, 2007). Redelmeier, Katz and Kahneman (2003) very elegantly used the positivist method of an RCT to demonstrate the importance of different realities which can exist even within single individuals, and the practical implications.

The methodology most closely associated with the interpretivist paradigm is qualitative research, with a variety of methods such as interviews or observations (Leavy, 2014). In qualitative research, bias is accepted as an unavoidable, and in fact essential, aspect of the reality being examined; instead of being avoided, it should be acknowledged and explored (Broom and Willis, 2007).

While positivism and interpretivism can be seen as the two major philosophical perspectives, both have been criticised and adapted in a variety of ways, leading to the wide range of epistemologies presented in Table 3.1. This plethora of possible paradigms to choose from can be overwhelming for the researcher, particularly as many of the paradigms overlap partially or have been developed specifically to refute other paradigms (Broom and Willis, 2007). Creswell and Plano Clark (2011) therefore advise that, in adopting a relevant paradigm, researchers should be guided by the aims of their research. In their model, the aims of a research project determine the paradigm, which in turn determines the methods.

3.3 From research aim to paradigm

The aim of this thesis is *"to provide key stakeholders in prehospital care with the information required to guide the funding and configuration of prehospital critical care for OHCA"* (Chapter 2). Of the five objectives outlined in the previous chapter, the first four are concerned with the effect of prehospital critical care on survival following OHCA and the associated monetary costs. These objectives lend themselves well to a positivist paradigm, where in the singular reality prehospital critical care for OHCA has a definite effect and a definite cost. Following an evidence-based medicine approach, an RCT and meta-analysis would be the resulting methods, followed by a cost-effectiveness analysis. However, limitations outlined in the Introduction chapter and the following chapters make this approach challenging, if not impossible. Current existing evidence suffers from confounding and bias, making a meta-analysis difficult and potentially misleading (von Vopelius-Feldt and Benger, 2016a). I entertained the possibility of undertaking a pilot-RCT of prehospital critical care for OHCA but a number of barriers, in particular ethical concerns, rendered this method unfeasible. Within the positivist paradigm, I felt that the best I could achieve (through my observational research design) was flawed results of little scientific value. The logical flow from aim to paradigm to method resulted in a dead-end. The solution was to start again from the beginning. The revised aim is to provide decision makers with information about prehospital critical care for OHCA, within the limitations and constraints of this thesis and the complex environment of prehospital critical care. Including these limitations in the aims allowed for a switch from the restraints of the positivist paradigm to a pragmatic paradigm.

3.4 Pragmatism

Pragmatism is a relatively young philosophical and research paradigm. Its proponents often seek to overcome the inflexibility of many existing paradigms and to actually de-emphasise the discussions around what the correct paradigm might be (McDermid, 2018; Pamental, 2013). From a philosophical point of view, pragmatism revolves around the following three key ideas (McDermid, 2018):

i) "An ideology or proposition is true if it works satisfactorily,"
ii) "The meaning of a proposition is to be found in the practical consequences of accepting it,"
iii) "And that unpractical ideas are to be rejected."

A good example of the pragmatic worldview is its rejection of Cartesian scepticism; the idea that we cannot confidently believe in an external world because we might merely be living in a dream (McDermid, 2018). To this, the pragmatist would say:

i) Believing in an external world works well most of the time.
ii) Believing in an external world has the practical consequences of not getting run over when crossing the road or hitting one's shin against the coffee table.
iii) If the Cartesian's are right and there is no external world, this reality would be just a dream without consequences. This proposition is neither helpful nor practical for the issues and questions which humanity faces.

The pragmatic ontology considers reality to be something to be negotiated and agreed on, depending on the question at hand, in order to come to useful conclusions (Broom and Willis, 2007). Metaphysical theories about hidden realities which can neither be proven nor disproven and do not result in practical consequences are seen as non-disagreements and should be abandoned (McDermid, 2018).

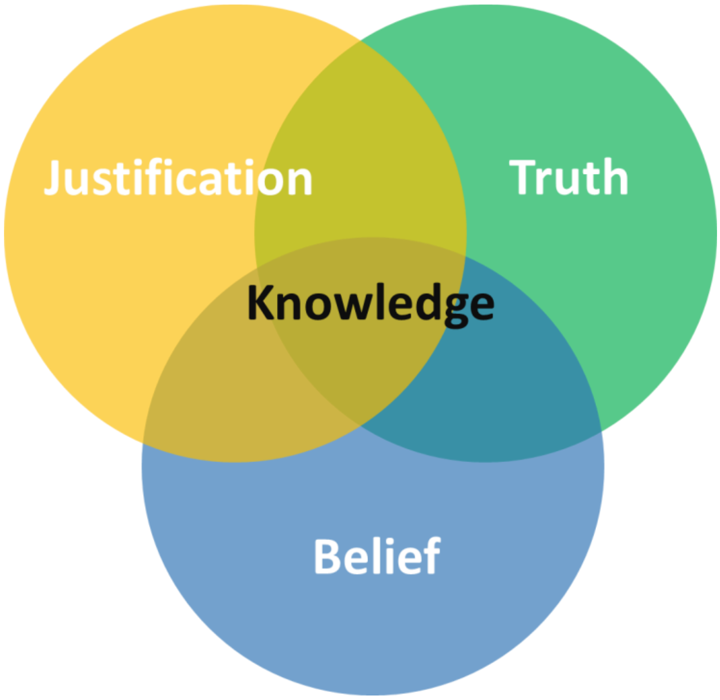
Epistemological theories are tools which can help us make sense of these realities. They are valued by their usefulness, rather than their origins or logical finesse, and are treated as working hypotheses which may need to be modified if new evidence or requirements develop (McDermid, 2018).

The methodology most closely associated with pragmatism is the mixed-methods approach, combining quantitative and qualitative research methods (Leavy, 2014). In the search for practical solutions, information from different sources of data, analysed with the appropriate method for each source, can be combined to provide the best possible answer. This pragmatic approach, focused on finding solutions that work despite less-than-perfect circumstances, can be found in the aims, objectives and methods of this thesis.

3.5 The Justified True Belief (JTB)

As described in the previous section, the pragmatic paradigm does not require the researcher to commit to a single epistemology, but allows for evaluation and selection of theories which prove useful to the cause. One such theory is the Justified True Belief; see Figure 3.2. The definition of knowledge as Justified True Belief, colloquially referred to as The JTB is not a particularly novel idea, nor is it perfect, as Gettier demonstrated (Nagel, Juan and Mar, 2013). From a pragmatic point of view, it is practical, easy to grasp and produces useful results in many situations. In order to for a person to know something, a person needs to believe it, have sufficient justification to believe it and, importantly, this justified belief also needs to be true in reality (note that the model assumes a singular reality in keeping with a positivist ontology).

Figure 3.2 The Justified True Belief



During the preparation and funding application phase of this thesis, I spent much time convincing people of the need for my observational research into the benefits of prehospital critical care for OHCA. There were two frequently encountered, dichotomous attitudes. On the one hand, a strong belief in the benefits of prehospital critical care, with the notion that the information that this thesis seeks to provide is not required. On the other hand scepticism regarding the validity and value of observational research in this area, with suggestions that this thesis wouldn't be able to provide useful results. The JTB helped me to structure my answers to both challenges.

1. **Truth**. Some truths are obvious and do not need to be proven. This point is probably argued most convincingly by Smith and Pell (2003) in their article *Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials.* In the case of prehospital critical care for OHCA however, the truth is very difficult to assess. In contrast to the parachute example, the intervention (prehospital critical care) and the outcome (survival) are separated by weeks of in-hospital treatment and there are significant confounders, making it impossible to ever clearly see the truth.
2. **Belief.** Many people hold strong beliefs in the benefits of air ambulances and the associated prehospital critical care teams. In the case of OHCA, this might be true. However, without solid justification, this would merely be a lucky guess. The main

problem with belief is that one can't argue with it and it is difficult to shift anybody's perception based solely on belief-based arguments.

3. **Justification.** Members of the panel that funded this thesis questioned the value of undertaking observational research to examine the effect of prehospital critical care on survival following OHCA. From a positivist perspective, a more definite answer to this question would require a RCT. I agree with the panel members that this thesis will not be able to deliver definite proof of benefit or no benefit from prehospital critical care for OHCA. However, it will provide some justification: data to inform discussion and information to guide future decisions. I can create estimates of worst/best case scenarios. Together with an estimate of probable costs, stakeholders can then have informed discussions, which might challenge and shift their current beliefs about the benefits and costs of prehospital critical care for OHCA.

It is with this pragmatic paradigm and the hope to provide information that allows readers to see things in a different way, that the next chapter embarks on a systematic review of the evidence with a narrative analysis of current research into the effects of prehospital critical care for OHCA.

4. A systematic review of the literature

4.1 Introduction

The preliminary evidence review, which supported the planning phase of this PhD thesis, identified only a small number of relevant studies (Olasveengen *et al.*, 2009; Mitchell *et al.*, 1997). It also identified a systematic review of the effects of prehospital physicians on outcomes after out-of-hospital cardiac arrest (OHCA) (Bottiger *et al.*, 2016). While the systematic review by Bottiger *et al.* (2016) is highly relevant, it did not specifically address the research focus of this thesis: prehospital critical care. Instead, it compared outcomes between prehospital care for OHCA by either physicians or paramedics. As discussed in Chapter 1, physician-delivered care is not synonymous with prehospital critical care; see Figure 1.12. In fact, many of the studies in the review by Bottiger *et al.* (2016) compare Advanced Life Support (ALS), delivered by physicians, with ALS or Basic Life Support (BLS) delivered by paramedics, and thus are not relevant to the topic of this thesis: prehospital critical care (Hagihara *et al.*, 2014; Dickinson, Schneider and Verdile, 1997). In contrast, the systematic review presented in this chapter specifically reflects the main research question of the thesis and is summarised in Box 4.1.

As described in Chapter 1, many aspects of OHCA have been extensively studied. A framework of definitions, known as the Utstein template, is helpful in guiding and structuring data collection and in comparing outcomes in OHCA research (Perkins *et al.*, 2015a; Cummins, 1991). See Chapter 1 for a detailed description of the Utstein template. Similarly, ALS care is based on international guidelines with only minimal regional variability (Link *et al.*, 2015; Soar *et al.*, 2015). In contrast, prehospital critical care to date has been poorly defined or standardised across developed Emergency Medical Services (EMS) systems, both in practice and in research (von Vopelius-Feldt and Benger, 2014a; Hyde *et al.*, 2012; Mackenzie *et al.*, 2009). The first challenge of this systematic review was therefore defining the I of the PICO acronym: population; intervention; comparator; outcome (Liberati *et al.*, 2009). I was able to use my own previous research to create a reproducible definition of prehospital critical care (von Vopelius-Feldt and Benger, 2014b). Importantly, this definition did not restrict prehospital critical care to physician-delivered care only; see Box 4.1 and Box 4.2.

With the anticipation of existing literature being sparse and largely observational, a narrative analysis and presentation of the evidence was chosen. This not only focused on the possible effects of confounding and bias on the overall findings of the review but also on how these sources of confounding and bias could be accounted for in my own research.

4.2 Methods

I employed a modified version of the evidence evaluation process used by the International Liaison Committee on Resuscitation (ILCOR) to create the foundation for their 2015 resuscitation guidelines (Morrison *et al.*, 2015). This modified approach consisted of:

1. PICOS question development
2. Iterative search strategy development
3. Article selection by two independent reviewers
4. Evidence review with focus on the risk of confounding and bias
5. Discussion and interpretation of findings

4.2.1 Inclusion and exclusion criteria

As discussed in Chapter 1, OHCAs occurring either due to trauma or in children tend to be caused by different pathophysiological processes and where therefore excluded from this review. Also in Chapter 1, I describe the different outcomes used to measure the quality of prehospital care for patients with OHCA. As return of spontaneous circulation (ROSC) is not a patient-focused outcome, I excluded studies which only reported rates of ROSC following OHCA. In regards to study designs, I excluded publications which described outcomes following prehospital critical care for OHCA without comparison to ALS care (e.g. case series or prehospital chart reviews). Box 4.1 summarises the inclusion and exclusion criteria, according to the PICOS structure. The PICO acronym is used frequently to ask precise clinical questions in evidence-based medicine (Hecht, Buhse and Meyer, 2016). For systematic reviews, an S is frequently added, representing the term study design(s) (Liberati *et al.*, 2009).

Box 4.2 summarises the interventions used to define prehospital critical care for this review; see Chapter 1 for a more detailed discussion of these interventions.

Box 4.1 Inclusion criteria according to the PICOS system

Patients	All cases of non-traumatic out-of-hospital cardiac arrest in adults (age 18 or older)
Intervention	Prehospital critical care by any provider group (paramedics or physicians) with interventional capacity beyond ALS algorithms and dedicated dispatch to critically ill patients*
Comparator	ALS by any prehospital provider
Outcomes	Any patient-focused outcome such as short or long-term survival or quality of life; ROSC alone was not considered a patient-focused outcome
Study designs	Any comparative design such as randomized trials, but also observational studies with a comparative element

**See Box 4.2 for detailed list of potential critical care interventions*
ALS: Advanced Life Support, ROSC: Return of spontaneous circulation

Box 4.2 List of prehospital critical care interventions for out-of-hospital cardiac arrest, based on previous research (von Vopelius-Feldt and Benger, 2014a)

Prehospital anaesthesia
Rapid sequence induction of anaesthesia (RSI)
Sedation or paralysis

Advanced cardiovascular management
Central intravenous access
Cardiac ultrasound
Thrombolysis
Non-ALS intravenous drugs (for example Magnesium, Calcium, Sodium Bicarbonate)
Use of vasopressors after return of spontaneous circulation

Special circumstances
Thoracostomy
Peri-mortem hysterotomy

ALS: Advanced Life Support

4.2.2 Search strategy

After initial consultation with a University of Bristol librarian, I created reproducible search strings (see Table 4.1) that were customised for searches in each of the following electronic databases: PubMed; EmBASE; CINAHL Plus and AMED (via EBSCO); Cochrane Database of Systematic Reviews; DARE; Cochrane Central Register of Controlled Trials; NHS Economic Evaluation Database; NIHR Health Technology Assessment Database; Google Scholar;

ClinicalTrials.gov. The wide spread of databases was chosen to optimise capture of grey literature, such as conference abstracts or government reports, as well as reliably identify higher level evidence such as randomised trials or existing systematic reviews.

Each search string was designed to meet the inclusion and exclusion criteria but also to balance sensitivity and specificity within each database. Therefore, the search strings for databases that returned only a few results on initial test searches consist of very broad categories, whereas searches within databases with large numbers of results (for example PubMed) were more restrictive. I tested for sensitivity of the more restrictive search strings by checking if known key publications (von Vopelius-Feldt, Coulter and Benger, 2015; Olasveengen *et al.*, 2009; Mitchell *et al.*, 1997) were identified by the search.

I excluded research published prior to 1990 as it was deemed very unlikely that this would be relevant to modern EMS practice. ALS guidelines are updated every 5 years and have changed significantly since pre-1990 (Link *et al.*, 2015; Chamberlain, 1989). Likewise, advances in technology and evidence-based medicine have changed practice and standards of prehospital care to a level that is not comparable to pre-1990 (Spaite *et al.*, 2014; Helm *et al.*, 1991).

Despite the fact that the review aimed to evaluate prehospital critical care by any provider, the search strategy reflects the fact that prehospital critical care is often provided by physicians or helicopter medical services (HEMS). Search terms such as doctor or helicopter were always used to broaden the search (OR syntax), rather than restricting it; see Table 4.1.

Also included in the results were all cited and citing articles of publications which were retrieved for full text analysis during the review process. In addition, I used social media requests (Twitter and Research Gate) to identify further grey literature. The final searches for each database were undertaken between April and June 2016. See Table 4.1 for a comprehensive overview of search strings, databases and search results.

Table 4.1 Literature search strategies and results

Database	Search strategy	Results
Pubmed	(prehospital emergency care[MeSH Terms]) AND cardiac arrest, out of hospital[MeSH Terms]	622
Pubmed	(pre-hospital OR prehospital OR EMS OR "emergency medical services" OR ambulance) AND (arrest OR sudden death) AND ("critical care" OR "intensive care" OR doctor OR physician OR HEMS OR helicopter)	1377
EmBASE	(pre-hospital or prehospital or EMS or "emergency medical services") and (arrest or "sudden death") and ("critical care" or "intensive care" or doctor or physician or HEMS or helicopter)	963
CINAHL Plus and AMED (via EBSCO)	(pre-hospital or prehospital or EMS or 'emergency medical services') AND (arrest or 'sudden death') AND (critical care or intensive care or doctor or physician)	359
Cochrane Database of Systematic Reviews	cardiac arrest	24
Database of Abstracts of Review of Effects (DARE)	cardiac arrest	70
Cochrane Central Register of Controlled Trials	(pre-hospital OR prehospital OR EMS OR emergency medical services) AND (arrest OR sudden death) AND (critical care OR intensive care OR doctor OR physician)	97
NHS Economic Evaluation Database	cardiac arrest	42
NIHR Health Technology Assessment Database	[MeSH] out-of-hospital cardiac arrest	2
Google Scholar (limited to 500 most relevant)	prehospital critical care out-of-hospital cardiac arrest	500
Clinicaltrials.gov	(prehospital OR pre-hospital OR EMS OR emergency medical services) AND (cardiac arrest OR sudden death)	133
Cited and citing articles of full text publications reviewed		365
Social media		0
Total		**4554**

4.2.3 Article selection

Article selection followed a three-step approach. First, two researchers (myself and co-supervisor JBR) independently reviewed all study titles and removed all publications which were obviously not related to the study question as well as duplicate results. Next, we independently reviewed the abstracts of all remaining publications, removing those that did not fulfil the inclusion criteria outlined in Box 4.1. Finally, both researchers independently reviewed the full text of all remaining publications to assess for inclusion in the final analysis. If there were discrepancies in the researchers' opinions during step one or two, the publication in question was moved forward to the next step. If there were discrepancies in step three, consensus was sought between the two researchers. If no consensus was achieved, a third researcher (supervisor JB) would have been asked to review the publication, however, this final step was not required for this review. The final full narrative analysis of all included manuscripts was undertaken by myself.

4.2.4 Analysis and presentation of results

The narrative analysis was undertaken in a three-step approach for each publication. First, I read each manuscript multiple times, to fully immerse myself in the research. I then extracted key aspects of each study into an evidence table, using the Strengthening The Reporting of Observational Studies in Epidemiology (STROBE) checklist (von Elm *et al.*, 2014) as guidance; see Table 4.2. Finally, I examined the publications for risk of bias and confounding, paying particular attention to sample size and population, differences in treatments or follow-up and methods of adjustments. Potential sources of bias or confounding for each study are presented in Section 4.4, together with descriptions of prehospital critical care and ALS care for each study. Care was taken to provide only a description of publications at this stage, rather than interpretation.

Finally, the overall reliability of the evidence, drawing on the findings of the evidence review, is discussed in Section 4.5. It also provides further interpretation of the systematic review findings by referencing other research and providing a wider context of the findings.

Overall, the systematic review was structured and presented according to the PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions (Liberati *et al.*, 2009). In keeping with good research practice, I prospectively registered the review with the International Prospective Register of Systematic Reviews (PROSPERO), registration number CRD42016039995.

4.3 Results

The search identified a total of 4,554 publications. After excluding duplicates and titles which did not meet inclusion criteria, 183 abstracts were reviewed, of which 27 full text manuscripts were retrieved for further assessment.

After review of the full text publications, three papers were eligible for inclusion in the systematic review (von Vopelius-Feldt, Coulter and Benger, 2015; Yasunaga *et al.*, 2010; Mitchell *et al.*, 1997). A further six full text publications did not include enough information to decide if EMS providers were practicing prehospital critical care and/or ALS. For five of these publications, I was successful in gaining this information by contacting the authors, resulting in two exclusions (Hagihara *et al.*, 2014; Dickinson, Schneider and Verdile, 1997) and three inclusions in the review (Hamilton *et al.*, 2016; Hiltunen *et al.*, 2016; Olasveengen *et al.*, 2009). The remaining study was excluded following a consensus decision within the research group (myself, JB and JBR). Based on our best interpretation of the information provided and our knowledge of the EMS system studied, we considered it unlikely that this publication from Taiwan compared prehospital critical care with ALS care (Yen *et al.*, 2006).

Reasons for exclusion of the other 18 publications after full text review were: comparison of prehospital critical care or ALS with BLS (4/18); all patients receiving critical care (3/18); non-experimental study designs such as systematic reviews (3/18); publications classified as editorials (2/18); comparing paramedics and physicians providing ALS (2/18). Two studies reported ROSC as the only outcome, one was a secondary review of previous research, and a further study examined the effect of in-hospital emergency physicians. All four of these publications were therefore also excluded.

Two conference abstracts also fulfilled the inclusion criteria and are included in the review (Seki *et al.*, 2014; Shiraishi and Otomo, 2014). The authors of the conference abstracts were contacted but I was unable to obtain further information.

See Figure 4.1 for a summary of the review process. Tables 4.2 and 4.3 provide an overview of key features of the included publications, which will be discussed in more detail in the following section.

Figure 4.1 Summary flow chart of the systematic review process

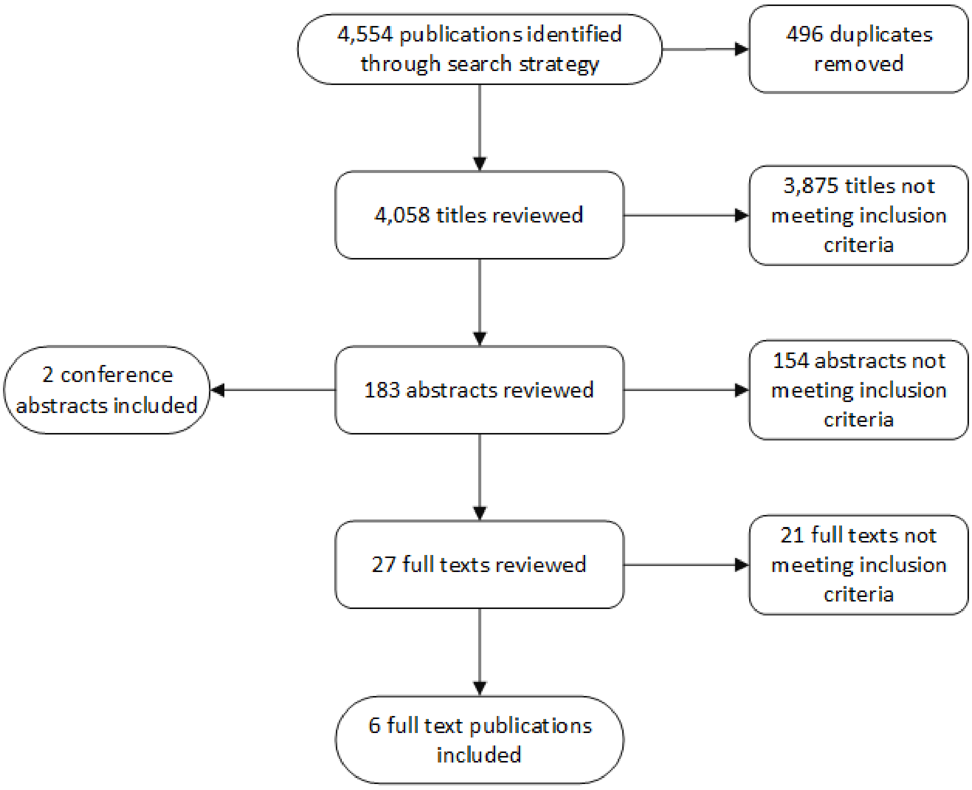


Table 4.2 Overview of included publications (continued on next page...)

Author	Year	Country	Study design	Population	Critical care	Comparator	Adjustments	Independent variables	Results
Mitchell *et al.* (1997)	Published 1997	USA and UK	Prospective, two single EMS	1,029 OHCA, urban and suburban	UK physicians with full resuscitation equipment (n=306)	US ALS-Paramedics (n= 723)	None	N/A	**Survival to hospital discharge** UK (physicians) 12.4% US (paramedics) 7.2%
Olasveengen *et al.* (2009)	2003-2008	Norway	Prospective, single EMS	1,128 OHCA, regional urban and suburban	Anaesthesiologists, board certified or last year of training (n=223)	ALS-Paramedics with yearly recertification (n=741)	Multiple logistic regression	Initial rhythm Therapeutic hypothermia Intubation Age Time from arrest to ALS Ambulance witnessed	**CPC1/2 at hospital discharge** OR 1.35 (0.75 to 2.60, p=0.36)
Yasunaga *et al.* (2010)	2005-2007	Japan	Prospective, nationwide	95,072 bystander-witnessed OHCA across Japan, with and without BCPR	Physicians with critical care capabilities Without BCPR (n=1,597) -With BCPR (n=1,961)	ELSTs trained to ALS level - Without BCPR (n=53,482) - With BCPR (n=38,077)	Logistic regression	Age Gender EMS response time Cardiac aetiology BCPR Initial rhythm	**1-month survival (OR)** No BCPR / BCPR ELSTs: OR 1 (reference) / OR 1.51 (1.43-1.59) Physicians: OR 1.63 (1.39-1.92) / OR 2.17 (1.89-2.49) **CPC1 at 1-month (OR)** No BCPR / BCPR ELSTs: OR 1 (reference) / OR 2.23 (2.05-2.42) Physicians: OR 1.18 (0.86-1.61) / OR 2.80 (2.28-3.43)
Hamilton *et al.* (2016)	2005-2012	Denmark	Retrospective, nationwide	21,165 OHCA, nationwide, including trauma	Specialists in anaesthesiology or intensive care (n=7,854)	BLS and ALS paramedics as well as nurse anaesthetists (n=7,854)	Propensity score matching	Gender Age Location (home or public) BCPR Initial rhythm Witnessed event Geographical location EMS response time Charlson comorbidity index	**1-month survival** OR 1.18 (1.04-1.34) **1-year survival** OR 1.13 (0.99-1.29)

Table 4.2 Overview of included publications (...continued)

Author	Year	Country	Study design	Population	Critical care	Comparator	Adjustments	Independent variables	Results
Hiltunen *et al.* (2016)	2010	Finland	Prospective, multiple EMS, urban and rural	614 OHCA, regional urban and rural, all ages and aetiologies	Specialists in anaesthesiology or intensive care (n=249)	ALS-Paramedics (n=246) BLS-Paramedics (n=119)	Multivariate analysis	Gender Initial rhythm Location (home or public) Witnessed event OHCA in presence of EMS Cardiac aetiology Dispatcher-recognised OHCA BCPR ALS- or BLS-paramedics Intubation or SAD Geographical location	**Survival to hospital discharge** OR 5.05 (2.94–8.68) **1-year survival** OR 2.57 (1.22–5.43)
von Vopelius-Feldt, Coulter and Benger (2015)	2012-2014	UK	Retrospective, single EMS	1,851 OHCA, regional urban and rural	Team of critical care paramedics and prehospital critical care physicians (n=165)	ALS-Paramedics (n=1,686)	Multiple logistic regression	Age Location (home, public or nursing home) Witnessed event BCPR EMS response time Initial rhythm	**Survival to hospital discharge** OR 1.54 (0.89 to 2.67)

UK: United Kingdom, EMS: Emergency Medical Services, OHCA: Out-of-hospital cardiac arrest, ALS: Advanced Life Support, OR: Odds ratio (95% confidence interval), CPC: Cerebral Performance Category, BCPR: Bystander CPR, ELST: Emergency Life Saving Technicians, BLS: Basic Life Support

Table 4.3 Overview of conference abstracts

Author	Year	Country	Study design	Population	Critical care	Comparator	Adjustments	Results
Seki *et al.* (2014)	2010	Japan	Prospective, nationwide	2,309 non-shockable OHCA with ALS interventions	Physicians (n not specified)	Paramedics (n not specified)	Multivariate logistic regression	**1-month survival** OR not specified (0.558-3.310) p=0.499
Shiraishi and Otomo (2014)	2012	Japan	Prospective, multicentre, regional	1,699 cases of witnessed OHCA in the Kanto region	Physicians (n=34)	Paramedics (n=34)	Propensity score matching	***"Favourable neurological outcome"* at hospital discharge** 5.9% (physician group) 5.9% (paramedic group) p=1.0

ALS: Advanced Life Support, OHCA: Out-of-hospital cardiac arrest, OR: Odds ratio (95% confidence interval)

4.4 Evidence review

4.4.1 Overview

Only limited information was available from the conference abstracts summarised in Table 4.3 (Seki *et al.*, 2014; Shiraishi and Otomo, 2014). I will therefore provide a brief summary of key aspects for each abstract, before then focusing exclusively on the full text publications.

Both abstracts present observational study designs and compared physician and paramedic care in Japan. Seki *et al.* (2014) included only cases of OHCA with non-shockable rhythm in their analysis and found no difference in 1-month survival between patients attended by prehospital physicians or paramedics. Shiraishi and Otomo (2014) used propensity score matching, resulting in matched groups of 34 cases (68 patients in total). No difference in outcome was found.

All full text publications in this review are observational studies, four of which used prospective data collection whilst two were retrospective. Sample sizes ranged from 614 to 95,072 cases. In five publications, prehospital critical care was provided by physicians; one study describes a model of physician and paramedic-delivered prehospital critical care. Three publications found better outcomes associated with prehospital critical care for OHCA, when compared to ALS, while the other three publications found no difference in outcomes. The full text publications are described individually, in chronological order in this section. In the following sections, I will discuss the quality and implications of this evidence for prehospital critical care for OHCA as well as its limitations.

4.4.2 Mitchell *et al.* (1997)

The first publication by Mitchell *et al.* (1997) compares the EMS systems of Edinburgh (United Kingdom, UK) and Milwaukee (United States of America, USA) and their impact on survival to hospital discharge after OHCA. In Edinburgh, prehospital critical care was provided by a physician-staffed mobile resuscitation team which responded to OHCA as a secondary response after initial resuscitation by BLS technicians or ALS paramedics. Physicians had access to *"full resuscitation equipment"* including a mechanical chest compression device, central venous access and anti-arrhythmic medication (Mitchell *et al.*, 1997, p.226). In contrast, Milwaukee provided a two-tier response to OHCA, with first response by BLS paramedics or firefighters, followed by ALS paramedics. The ALS paramedics were able to intubate and administer intravenous drugs. They could also pronounce life extinct after consultation with the directing physician. Survival to hospital discharge rates were significantly higher in the UK compared to the USA (12.4% and 7.2% respectively, $p<0.01$). However, rates of witnessed cardiac arrests and bystander CPR were also significantly higher in the UK, compared to the USA (65.7% vs 25% and 42.3% vs 27.1%, respectively, $p<0.001$). The rates of shockable first rhythm was 52.3% in the UK and 43.4% in the USA (statistical significance not specified). Median response times for first EMS response was 8 minutes in the UK and 6 minutes in the USA, ($p<0.0001$). No statistical adjustments were undertaken to address this imbalance of prognostic factors, but the authors noted that when only witnessed OHCAs with shockable rhythm were compared (n=129 and n=106 for UK and USA, respectively), there was no statistically significant difference in outcome (23.3% vs 17% in the UK and USA, respectively, $p>0.05$).

4.4.3 Olasveengen *et al.* (2009)

Olasveengen *et al.* (2009) compared rates of hospital discharge with favourable neurological outcome, defined as Cerebral Performance Category (CPC) 1 or 2. The city of Oslo had a one-tiered response to OHCA, which consisted of either ALS-paramedic or physician-staffed ambulances. The ALS-paramedics underwent yearly ALS- recertification and all undertook shifts on the physician-staffed ambulance as part of a quality improvement project. The prehospital physicians were senior anaesthesiologists, who were able to provide prehospital anaesthesia (personal correspondence with the author).

Prehospital physicians were first on scene in about 20% of all OHCA. These cases had significantly more favourable prognostic factors such as OHCA in public, bystander CPR and shockable rhythm. After adjusting for this imbalance, using multiple logistic regression, no significant difference in the rate of discharge from hospital with CPC 1 or 2 was observed between the physician and paramedic groups (OR 1.35, 95% CI 0.71-2.60). The authors also describe a group of 155 patients where prehospital physicians were requested as second responders. These were excluded from the analysis as they contained an unknown number of paramedic requests for support with post-ROSC treatment and as such would have introduced bias. The unadjusted rates of discharge from hospital with CPC 1 or 2 were 16% in this group, compared to 10% and 13% in the ALS-paramedic and primary response physician groups, respectively.

4.4.4 Yasunaga *et al.* (2010)

With just over 95,000 cases, the largest study was undertaken by Yasunaga *et al.* (2010), who used data from a national cardiac arrest registry in Japan. Of note, only witnessed OHCAs were included in the analysis. The prehospital care for OHCA in this study was a one-tiered system of ALS-trained Emergency Life-Saving Technicians (ELSTs). A few regions also dispatched prehospital physicians to suspected OHCA; this was the case in 3.7% of all OHCA patients recorded in the registry. The ELSTs were able to insert a supraglottic airway, gain intravenous access and administer intravenous fluids and Adrenaline. Critical care interventions available to prehospital physicians included central venous catheterisation, infusion of catecholamines, anaesthetic drugs and fibrinolytic agents.

Outcomes were adjusted for prognostic factor imbalance, using logistic regression. The authors compared four interventional groups: ELST care without bystander CPR (reference); ELST care with bystander CPR; physician care with bystander CPR; physician care without bystander CPR. Bystander CPR significantly increased rates of 1-month survival and good cerebral performance at 1 month. Physician presence showed a significant association with 1-month survival. However, for the outcome of good cerebral performance (CPC 1) at 1 month, the 95% confidence intervals overlapped with those of the ELST groups; see Table 4.2. At the same time, there was a higher proportion of patients in vegetative status or brain dead at 1 month in the physician groups compared with the paramedic groups. In a subgroup analysis of 11,970 patients with initial shockable cardiac rhythm, physician presence was associated with significantly higher rates of 1-month survival and good cerebral performance (CPC 1) at 1 month, in all groups. The authors point out that prehospital physicians in their study are generally attached to and admit their patients to hospitals which *"typically provide more optimal post-return of spontaneous circulation treatments, including therapeutic hypothermia and percutaneous coronary intervention"*, and this may be a significant confounding factor (Yasunaga *et al.*, 2010, p.2).

4.4.5 Hamilton *et al.* (2016)

Hamilton *et al.* (2016) provided the second largest dataset with 21,165 cases of OHCA of all aetiology, including trauma. In the Danish EMS system, an ambulance staffed with either BLS-technicians or ALS-paramedics was dispatched to OHCA. A mobile critical care unit was also dispatched at the same time and was staffed either by specialists in anaesthesiology or critical care (63% of cases), or by nurse anaesthetists and ALS-paramedics. Prehospital physicians provided general anaesthesia and cardiovascular support and also had access to ultrasound for the later period of data collection (private correspondence with the author). ALS-paramedics and nurse anaesthetists were able to administer intravenous drugs under standing orders, nurse anaesthetists were also able to intubate.

Prognostic factors were unequally distributed, favouring survival in the physician group. Propensity score matching was therefore undertaken, based on Utstein variables, but also included pre-OHCA morbidity measured by the Carlson Index. This resulted in a comparison between 7,854 cases in each matched group. One-month survival was positively associated with prehospital physician care with an OR of 1.18 (95% CI 1.04-1.34). Secondary outcomes showed non-significant trends towards improved outcomes in the physician group with ORs for one-year survival and ROSC of 1.13 (95%CI 0.99-1.29) and OR 1.09 (95%CI 1.00-1.19), respectively.

4.4.6 Hiltunen *et al.* (2016)

Hiltunen *et al.* (2016) undertook an observational study with the primary aim of associating airway management during OHCA in Southern Finland with survival to hospital discharge and one-year survival. The Finnish EMS system provided a three-tiered response to OHCA, with BLS and ALS-trained prehospital emergency care nurses, followed by a third tier of prehospital physicians who were specialists in anaesthesia and critical care. Prehospital physicians attended 41% of OHCA and were able to provide general anaesthesia and cardiovascular support.

The authors used multivariate analysis to evaluate the effects of supraglottic airway management and endotracheal intubation during OHCA. This also included a variable of prehospital physician presence which showed a significant association with both survival outcomes; see Table 4.2. Given that the focus of the paper is on airway management rather than prehospital physicians, only limited information is available regarding the patient characteristics in the physician and paramedic groups. The authors also note that prehospital physicians responding to OHCA can be stood down by the first or second tier response unit, when resuscitation appears futile.

4.4.7 von Vopelius-Feldt, Coulter and Benger (2015)

The most recent publication is one for which I am the first author and used data from a regional EMS system in the UK, from 2012 to 2014 (von Vopelius-Feldt, Coulter and Benger, 2015). The standard EMS response to OHCA is ALS-trained paramedics, but during the study period a prehospital critical care service also attended approximately 9% of OHCAs. UK paramedics are trained and certified to follow the ALS algorithms, including intubation or use of a supraglottic airway and intravenous drug therapy. The critical care team consisted of a mix of critical care paramedics and prehospital physicians and was capable of interventions such as prehospital anaesthesia and the administration of antiarrhythmic and inotropic drugs (von Vopelius-Feldt and Benger, 2014b).

Due to targeted dispatch of the critical care team, patients in the critical care group had significantly more positive prognostic factors for survival from OHCA than the ALS paramedic group. After adjusting with multiple logistic regression, there was no significant difference in survival to hospital discharge between the two groups (OR 1.54, 95%CI 0.89-2.67). Due to the small sample size (165 cases in the critical care group), a type-two error is a possibility in this study.

4.5 Discussion

There is limited evidence to support prehospital critical care for OHCA. This literature review identified two conference abstracts which show no benefit from prehospital critical care, however these are difficult to interpret due to the limited information available. Of the six observational studies included, three studies demonstrated an association between prehospital critical care and improved outcomes after OHCA (Hamilton *et al.*, 2016; Hiltunen *et al.*, 2016; Yasunaga *et al.*, 2010). The other three studies did not demonstrate any difference in patient-centred outcomes after OHCA when comparing prehospital critical care with ALS (von Vopelius-Feldt, Coulter and Benger, 2015; Olasveengen *et al.*, 2009; Mitchell *et al.*, 1997). I believe that the conflicting findings can be at least partially explained by study design and the logistics of prehospital care for OHCA.

4.5.1 The question of adequate sample size

A potential reason why no benefit from prehospital critical care for OHCA was found might be a type-2 error due to small sample sizes. The three negative studies have a combined sample size of 3,214 after adjustment (von Vopelius-Feldt, Coulter and Benger, 2015; Olasveengen *et al.*, 2009; Mitchell *et al.*, 1997). Likewise, the sample sizes of the conference abstracts range from 64 to 2,309.

Olasveengen *et al.* (2009) calculated that a sample size of 8,000 would be required to demonstrate a statistically significant difference in outcome in their patient population. Similarly, my own pilot study showed that a sample size of about 6,000 would be required to detect an absolute improvement in survival of 3.5% with a power of 0.8 (von Vopelius-Feldt, Coulter and Benger, 2015). It is therefore possible that the conflicting findings are attributable to a type-2 error, with the three publications in support of prehospital critical care having a combined sample size of 111,394 (Hamilton *et al.*, 2016; Hiltunen *et al.*, 2016; Yasunaga *et al.*, 2010).

Given that the sample size of publications in support of prehospital critical care is more than 30-fold larger than that of negative studies, should we accept that prehospital critical care improves outcomes after OHCA? Before drawing any conclusions, it is important to also consider the logistics of providing prehospital critical care, particularly the dispatch, destination hospital and training of EMS providers for OHCA.

4.5.2 Confounding by indication

Despite a moderate sample size of 614 cases of OHCA, Hiltunen *et al.* (2016) describe a highly significant association between prehospital physician presence and mid- and long-term survival (Hiltunen *et al.*, 2016). However, the authors advise caution when interpreting these results. Dispatch of the prehospital physicians in this Finnish EMS system frequently depended on information provided by the first EMS resources at scene. For OHCA, the physician team might decide not to attend cases that were deemed futile, *"due to extensive time from collapse to EMS arrival, unsuccessful resuscitation efforts, and the presence of comorbidities"* (Hiltunen *et al.*, 2016, p.3).

Targeting the limited resource of prehospital critical care to patients with the highest likelihood of benefit is a sensible strategy. However, when it comes to researching the benefit of prehospital critical care for OHCA, it introduces confounding by indication, where patients with better prognostic factors for survival are more likely to receive prehospital critical care than those with a worse prognosis (Fouche and Jennings, 2016). In this review, within all publications that compare prehospital critical care with ALS in the same EMS system, the critical care group had better prognostic factors (Hamilton *et al.*, 2016; Hiltunen *et al.*, 2016; von Vopelius-Feldt, Coulter and Benger, 2015; Yasunaga *et al.*, 2010; Olasveengen *et al.*, 2009). While all of these publications use statistical methods to adjust for this imbalance, there is a strong possibility that unmeasured residual confounding factors biased the results in favour of prehospital critical care.

4.5.3 Different in-hospital treatment of out-of-hospital cardiac arrest

Another factor that might influence reporting of outcomes in favour of prehospital critical care is in-hospital treatment. Yasunaga *et al.* (2010) demonstrated significant associations between prehospital physician attendance for OHCA and increased survival. However, the authors also clarify that prehospital physicians in their study are more likely to admit patients to hospitals providing higher levels of care following OHCA. Similar scenarios exist in some of the other publications. In my own study, prehospital critical care teams admitted 82% of their post-ROSC patients to a regional cardiac centre, compared to a 20% admission rate to the cardiac centre for ALS paramedics (von Vopelius-Feldt, Coulter and Benger, 2015). In the study by Hamilton *et al.* (2016) from Denmark, 39.3% of cases attended by prehospital physicians occur within a metropolitan area, compared to 14.8% in the non-physician group. Patients receiving prehospital critical care in these studies are therefore more likely to receive early coronary angiography, targeted temperature management and treatment in high volume centres, all of which have been linked to better outcomes (Dumas *et al.*, 2016; Schober *et al.*, 2016; Nielsen *et al.*, 2013).

4.5.4 Potential benefits of prehospital critical care

Finally, the training, experience and governance structure of EMS providers needs to be considered when comparing prehospital critical care and ALS for OHCA. In all full text publications in this review, prehospital critical care was provided by senior specialist physicians and, in the pilot study for this project, also by specially trained critical care paramedics (von Vopelius-Feldt, Coulter and Benger, 2015). It is likely that these critical care providers can improve care for OHCA through a combination of critical care procedures, provider experience and triage to the most appropriate hospital (von Vopelius-Feldt and Benger, 2016b).

While many prehospital critical care procedures require significant training and expertise, others can be integrated into ALS provider care through new equipment or guidelines (von Vopelius-Feldt and Benger, 2014b). In our local service, capnography-guided resuscitation and the use of vasopressors for hypotensive post-ROSC patients were initially restricted to critical care providers, but have since been integrated into ALS-paramedic practice (Brown *et al.*, 2016; von Vopelius-Feldt and Benger, 2014b).

The experience of ALS paramedics has been shown to have a significant association with survival after OHCA in a large Australian study (Dyson *et al.*, 2016). Prehospital critical care providers will be highly experienced in the care of critically ill patients, including OHCA, through their practice in hospital or as a result of targeted dispatch to cases of severe illness or injury (Hamilton *et al.*, 2016; von Vopelius-Feldt, Coulter and Benger, 2015). In addition, prehospital critical care services often provide advanced clinical governance structures with regular case reviews and quality improvement projects, which might not be available to the cohort of ALS providers (von Vopelius-Feldt and Benger, 2013).

Finally, prehospital critical care providers potentially have more freedom to select destination hospitals, such as cardiac or trauma centres, as appropriate for each patient (von Vopelius-Feldt, Coulter and Benger, 2015).

All of these aspects make it possible that prehospital providers can achieve better outcomes for an individual patient following OHCA (Hamilton *et al.*, 2016; Hiltunen *et al.*, 2016; Yasunaga *et al.*, 2010). However, prehospital critical care providers can potentially benefit not just the one patient in their care, but their entire EMS system. Demonstrating excellence in care, trialling new procedures and interventions, implementing guidelines and training as well as providing feedback and mentoring all have the potential to improve care for OHCA throughout the entire EMS system (Cushman *et al.*, 2010; Olasveengen *et al.*, 2009).

It is very encouraging that Hamilton *et al.* (2016) showed an overall improvement in survival after OHCA from 5.8% in 2005 to 11.5% in 2012. Importantly, this increase was seen in both the prehospital physician group and the paramedic group. In fact, when comparing only data from the latter years of data collection (2009-2012), there was no statistically significant difference in outcomes after OHCA, when comparing prehospital physicians and paramedics. This is due to a more pronounced improvement in survival rates in the ALS paramedic group compared to the prehospital physician group, as shown in Figure 2 of the publication. While Hamilton *et al.* (2016) do not discuss reasons for this reduction in the difference in survival rates over time, it is likely that the Danish EMS system used some aspects of quality improvement of ALS care during the course of the study. Current evidence regarding the treatment of OHCA suggests that the optimisation of early and basic interventions, such as CPR, ambulance response times and defibrillation is more effective in improving survival than the introduction of complex interventions at a later stage of the Chain of Survival, such as prehospital critical care (Jentzer *et al.*, 2016).

4.6 Challenges and Limitations

4.6.1 Systematic confounding

This review identified only studies with observational research designs, which raises the possibility of bias and confounding. Of particular concern is the fact that the sources of potential bias and confounding in the individual studies would invariably favour the intervention group of prehospital critical care. To control for this, one publication presented a subgroup analysis of only witnessed OHCA with a shockable rhythm (Mitchell *et al.*, 1997), four studies used regression methods (Hiltunen *et al.*, 2016; von Vopelius-Feldt, Coulter and Benger, 2015; Yasunaga *et al.*, 2010; Olasveengen *et al.*, 2009) and one publication used propensity score matching (Hamilton *et al.*, 2016). While all the publications which used statistical methods of adjustments included important predictors of survival (see Table 4.2), only one publication reported measures of robustness of the statistical model, an important consideration of internal validity (von Vopelius-Feldt, Coulter and Benger, 2015).

4.6.2 Heterogeneity of EMS systems

There was considerable heterogeneity in sample sizes, study populations and EMS systems' configurations between the studies, making meta-analysis inappropriate. Confounding and bias of the full text publications are possible and discussed in Section 4.5, however, I was unable to obtain further information for the conference abstracts.

Both the intervention of prehospital critical care and the comparator of ALS vary in configuration in the EMS described in this review. There is limited information on the modes of dispatch, response times and interventions delivered by prehospital critical care teams. Likewise, ALS care will have varied between countries and has also developed and changed significantly over the course of the last 20 years. This heterogeneity makes the overall results difficult to generalise, and certain publications might be more relevant than others for individual readers, depending on the configuration of their local EMS system. This limitation applies in particular to EMS systems where prehospital critical care is delivered by paramedics, as only one publication in this review describes a system of paramedic and physician prehospital critical care (von Vopelius-Feldt, Coulter and Benger, 2015), with the other five studies focusing exclusively on EMS physicians.

4.6.3 Social media search strategy

Emergency medicine, critical care medicine and many areas of research have seen a significant incorporation of social media into daily practice (Cameron *et al*., 2017). In evidence-based medicine (EBM), social media is used to accelerate dissemination of evidence, to publicly appraise research and to guide clinicians to relevant resources, often referred to as FOAM (free open access medical education) (Weingart and Thoma, 2015).

From the researcher's perspective, social media use is encouraged by universities and employers to raise the profile of the researcher and institution, to disseminate findings and to engage with public debate. In this spirit, I included social media in the search strategy of the systematic review. Of note, the request for information posted on Twitter did not produce a single result, as shown in Table 4.1. Possible reasons for this disappointing result are the topic of prehospital critical care being rather niche and the only moderate amount of people who follow me on Twitter; see Figure 4.2. Given the minimal effort required to post a request for information, other researchers may wish to include social media strategies in the systematic search for evidence, but need to consider the effect of their digital network's size and activity on return of information.

Figure 4.2 Screenshot of Twitter account @JVopelius, June 2016

4.7 Conclusions

Prehospital critical care has the potential to improve survival after OHCA. While there is some observational research to support this hypothesis, sources of bias limit the conclusions that can be drawn. On the other hand, studies that show no benefit from prehospital critical care

are limited by inadequate sample sizes. With randomised controlled trials unlikely to gain ethics committee approval, the benefits of prehospital critical care need to be proven through the use of large and detailed databases with sophisticated statistical adjustment to control for as many potential confounders as possible.

4.8 What next?

The findings of this systematic review highlight issues relating to observational research in this area and have informed the methods and interpretation of this thesis. The first question that needs to be addressed, however, is the relevance of the results of this systematic review to the research question.

The focus of this thesis is to evaluate the potential benefits of prehospital critical care, delivered by highly specialised providers, working in a system where ALS care is well established. Typical examples of EMS systems with these configurations are today found in the UK, Australia and North America. With the exception of the pilot study to this thesis (von Vopelius-Feldt, Coulter and Benger, 2015), none of the publications in this review can be applied directly in this context. The ALS providers in the studies are frequently only trained to undertake partial aspects of ALS and/or require telephone authorisation prior to certain treatments. A detailed discussion of ALS provider competencies is beyond the scope of this chapter, but it is possible that ALS paramedics in the UK are trained to a somewhat higher standard than the ALS care described in the overall review (Brown *et al.*, 2016; von Vopelius-Feldt and Benger, 2014b).

Another important point to note is that the publications (with the exception of the pilot study) did not set out to evaluate prehospital critical care for OHCA, but to examine the effect of EMS physicians. While there is a significant overlap between prehospital critical care and EMS physician care, the models are not always interchangeable. The findings of this review regarding the benefits of prehospital critical care are therefore somewhat implicit and dependent on the definition described in Section 4.2. It is unclear how similar the configurations of EMS physician care are to the prehospital critical care models that will be examined in this thesis.

This limitation has important implications for the design of the research presented in the following chapters. None of the publications provided a detailed description of what prehospital critical care after OHCA actually consisted of. In fact, three of the publications in the systematic review could only be included after correspondence with the authors and brief descriptions of the EMS physicians' care that is delivered after OHCA. From the beginning, the research protocol for this thesis included an analysis of interventions undertaken by the prehospital critical care providers when attending OHCAs, based on peer review and feedback resulting from the pilot study. Based on the systematic review, this will be the first study to provide this level of detail and will be valuable for interpretation and generalisation of the findings.

The second major implication of the findings of this systematic review is the issue of bias and confounding in observational research in general and, in particular, when addressing the question of prehospital care for OHCA. Other than the need to control for the known prognostic factors of survival (based on the Utstein variables), the systematic review highlighted issues of targeted dispatch of prehospital critical care teams and differences in hospital treatment. Both of these factors are addressed in the research protocol for my own observational research. Nevertheless, every known (and probably most unknown) sources of bias and confounding in these publications systematically favours EMS physicians and/or prehospital critical care. Therefore, any finding of significant improvement in survival after OHCA with prehospital critical care, resulting from this thesis, will need to be carefully scrutinised and critically reviewed, to consider the extent to which it is likely to be attributable to residual confounding.

Of course, the most obvious strategy to avoid the issue of bias and confounding is randomisation. By leaving patient allocation to chance rather than to implicit and explicit decision making at the point of dispatch, all known and unknown variables that influence outcome should be equally balanced between the prehospital critical care and the ALS care groups. Unfortunately, randomising a potentially life-saving resource without patient consent is ethically challenging (Bottiger *et al.*, 2016) and this approach was rejected by the patient and public involvement group which advised during the planning phase of this thesis. Given the lack of clear evidence to support prehospital critical care, I will further explore the ethical, practical and financial considerations regarding research of prehospital critical care for OHCA in my qualitative research presented in the next chapter.

5. Original research: A qualitative analysis of stakeholders' views on research and funding of prehospital critical care for out-of-hospital cardiac arrest

5.1 Introduction

A complex healthcare intervention can be described as one which contains several interacting components (Craig *et al.*, 2008). This is certainly true for prehospital critical care, where potential benefits for patients could result from any combination of interventions, provider expertise or mode of transfer to hospital (von Vopelius-Feldt, Coulter and Benger, 2015). The unpredictable nature and geographic challenges of prehospital emergency care and the involvement of charities in the funding of prehospital critical care create a complex environment in which to undertake this research (McClelland *et al.*, 2015).

In addition to the intervention and the environment, the nature of out-of-hospital cardiac arrest (OHCA) adds further complexity. Patients are unable to provide consent during the prehospital phase, and treatments must be provided within minutes (van Belle *et al.*, 2015). On the other hand, meaningful outcomes often cannot be measured until weeks or months have passed and are significantly influenced by patient factors and also hospital treatment (Andrew *et al.*, 2017).

Finally, prehospital critical care, while largely unproven, has already been implemented in many parts of the United Kingdom (UK) (Hyde *et al.*, 2012), which may reflect a perceived lack of equipoise.

The Medical Research Council recommends researchers evaluating complex interventions to "*involve stakeholders in the choice of question and design of the research to ensure relevance"* (Craig *et al.*, 2008, p.13). Furthermore, this guidance document encourages researchers to *"always consider randomisation, because it is the most robust method of preventing […] selection bias"* (Craig *et al.*, 2008, p.10). In the planning process for this thesis, I discussed potential research designs and general ethical issues with: a patient and public involvement (PPI) group that had been set up some years previously to provide input and advice to OHCA research; other researchers; service funders; clinical colleagues working in Emergency Medical Services (EMS). Finally, the research design was subject to strict peer review when the project was submitted for funding by the National Institute for Health Research (NIHR).

During this process, I noted how the different stakeholder groups disagreed strongly about the ethical acceptability of randomising the intervention of prehospital critical care for OHCA, the information that is required to direct healthcare funding and even the need to research the question at all. Given the importance of undertaking stakeholder-relevant research, I decided to include a formal examination of these stakeholders' views in this thesis, with particular focus on randomisation.

The initial idea for this qualitative research was that, by eliciting each stakeholder group's view on randomisation of prehospital critical care for OHCA, obstacles could be identified and an agreement could be reached on how such a study might be undertaken. This information could then also be used as a framework for randomisation in similarly challenging areas of research. A combination of the initial findings of the observational research presented in Chapter 7 and the framework for randomisation generated in this chapter could then form the foundation for a future randomised controlled trial of prehospital critical care following OHCA.

In Section 5.2 I will describe how this initial aim needed to be adjusted early during the course of the research, due to unexpected findings during the first focus group discussion. As a result, the scope of this research was widened to include additional aspects of stakeholders' views, as discussed further in Section 5.2.2.

5. 2 Methods

5.2.1 Researcher bias/epistemology

The ontology and epistemology which underpin this thesis are discussed in detail in Chapter 3. Given the importance of underlying paradigms, particularly in qualitative research (Caelli, Ray and Mill, 2003), I will briefly discuss the background of all individuals involved in this phase of the thesis and the paradigms considered and chosen.

The researcher team for this aspect of the thesis consisted of Jonathan Benger (JB, director of studies), Janet Brandling (JBR, co-supervisor) and myself. JB and myself work as emergency medicine physicians and have published largely quantitative research with an underlying positivist epistemology (Benger *et al.*, 2016; von Vopelius-Feldt, Coulter and Benger, 2015). JBR is a research fellow who has focused on qualitative research in a variety of healthcare settings (Harrison and Brandling, 2009) and has previously worked with JB on a qualitative study in prehospital care (Brandling *et al.*, 2016).

This thesis is a combination of the exploration of stakeholders' views presented in this chapter and the quantitative analysis of the effects and costs of prehospital critical care following OHCA. The epistemology adopted for the thesis as a whole is pragmatism, allowing for flexibility, frequently required in the less controlled prehospital care environment (Perkins *et al.,* 2015c).

Creswell and Plano Clark (2011) argue that a preferred approach in mixed methods is to adjust philosophical paradigms to the different phases of the research. In keeping with this idea, I considered two other common paradigms used in qualitative or mixed methods research: interpretivism and post-constructivism.

Interpretivism seemed initially attractive due to its ontological assumption that more than one reality exists and that they are socially and experimentally constructed (Guba and Lincoln, 1990). However, the focus on lived individual experience, while certainly interesting in regards to survivors of OHCA and prehospital providers, was not seen as particular applicable to other stakeholder groups or in keeping with the focus of the research question.

Post-constructivism, on the other hand, is frequently used in policy research where tangible results are required (Pratt, 2003). The underlying ontology is one of warranted assertability, which proposes the existence of one true reality, which can only be perceived imperfectly due to unobservable data (Denzin and Lincoln, 2000). This paradigm was prominent during the planning of the qualitative research phase. I assumed that through discussion and compromising, I would identify a right way of conducting research in the field of prehospital critical care, balancing the different stakeholder requirements. However, after the first few interviews, it became clear that stakeholder groups had such diverse views on key topics that such common ground would be difficult to identify. Within a post-positivist paradigm, I would have had to declare some stakeholders' views as less representative of the truth and, therefore, less valid than others' (Creswell and Plano Clark, 2011). Such a ranking of views was neither intended in the aims of the research, nor would it have been useful or externally valid.

I therefore chose a paradigm which matched the aim of this phase of the PhD thesis; a process suggested by Creswell and Plano Clark (2011). Pragmatism allowed me to respect stakeholder groups' perspectives while exploring common underlying mechanisms, to combine analysis of preconceived (deductive) and emerging (inductive) themes over the course of data collection. In addition, I used a pragmatic approach to participant selection and data collection, as discussed in the next section.

5.2.2 Developing the protocol

5.2.2.1 Changes in aims and objectives

The initial objective of this qualitative phase of the PhD project was *"to explore the barriers to a randomized trial in this area and consider how they could be overcome".* I had envisaged that the stakeholder discussions would provide a somewhat retrospective justification for doing an observational study, while also creating a roadmap to a potential future randomised trial which would satisfy all stakeholders' concerns. In my mind, the likely solution on which participants would agree was a trial using cluster-randomisation or a stepped-wedge design, gradually introducing prehospital critical care for OHCA. While this would be technically and financially extremely challenging, it should have been ethically defensible as patients would receive, on average, a higher level of care.

However, the plan of finding consensus did not last longer than the first focus group discussion with the PPI group, who vehemently rejected any form of randomisation. This first discussion also revealed differences not just in opinions on research, healthcare and funding but also far-ranging differences in the underlying ontological perspectives of what a critical care team is, what fairness is, and whether OHCA could be treated like any other condition. Following this first focus group discussion, it became obvious that the initial aim of an agreement on a specific randomisation procedure was very unlikely to be achievable, and that the focus on this very technical aspect of prehospital research was too narrow.

I therefore redefined my aims and objectives in the light of these initial and unexpected findings. The aim shifted from finding a solution for researchers like myself, to understanding the range of opinions that were held by these varied and enthusiastic groups of stakeholders, and how these opinions developed from common starting points to such different end points. The scope of the research was widened and, while still focusing on randomisation, also included views on priorities of prehospital research and resource allocation. The aim of the research presented in this chapter is therefore to answer the following questions:

- What are stakeholders' priorities for prehospital research?
- What are stakeholders' views on randomisation of prehospital critical care, and what are the underlying principles?
- How do stakeholders consider allocation of resources in prehospital care?

5.2.2.2 Changes in the data collection process

Before beginning the research, I had identified focus group discussions as the most appropriate method of data collection. Focus groups have been used extensively in market research and are used frequently in stakeholder engagement projects in healthcare (Krueger and Casey, 2015). The strengths of focus group discussions in qualitative research are found in the interaction between participants, which can produce rich data. They are also useful in situations where consent between different stakeholders is required (Krueger and Casey, 2015). The project started out with a focus group discussion with the PPI group.

However, I failed in the attempt to arrange a focus group with the next stakeholder group (charity representatives). I had managed to elicit enough interest from key individuals to conduct a group discussion at a national conference, but due to busy schedules and keen interests in the actual conference contents, I was unable to arrange a time and place that suited a sufficient number of potential participants. Instead, I used the conference to confirm interest of participants and arranged to meet them individually for face-to-face interviews.

The interviews and focus groups followed the same semi-structured question guide and topics but each method has its distinct advantages and disadvantages, as summarised in Table 5.1. This change in approach was discussed within the supervision team and we accepted that this was part of a pragmatic research approach and further data collection from stakeholder groups should be undertaken in whichever format was most feasible. We agreed that I would need to monitor for any significant differences which might arise from the mixing of data collection methods. The result of this monitoring are presented in Section 5.5.1.

Table 5.1 Comparison of focus group discussions and interviews, based on Krueger and Casey (2015)

Criteria	**Focus group**	**Interview**
Group interaction	+++	-
Power imbalance in favour of researcher	-	++
Exploration of consensus (or lack of)	++	-
Opportunity to discuss sensitive subject	+	++
Peer pressure for conformity	++	-
In-depth exploration of Individual views	+	++
Efficiency of conduct	++	-
Ease of recruitment and conduct	+/-	++

Strength of features present in data collection methods: +++ very strong; ++ strong; + weak; - absent

5.2.3 Participant selection

Stakeholder groups were identified a priori, based on my experience with the PPI group and the peer review process that occurred in the preparation phase of this thesis. After discussion with the supervision team, we agreed to include five key stakeholder groups. For each group, I aimed for four to 10 participants in the focus groups and four to six participants in interviews. In order to allow stakeholders to comfortably express their opinions and to fully explore each stakeholder group's view, I chose to undertake data collection in homogenous groups, rather than mixing participants from different stakeholder groups in the same focus group. This decision was based on the strength of opinions and emotive reactions of stakeholders, encountered in the discussions with stakeholders during the preparation phase. In keeping with a pragmatic approach, the participant recruitment process was tailored to each group and followed a convenience sampling strategy, aimed at optimising efficient recruitment of information-rich cases (Palinkas *et al.*, 2015). The stakeholder groups and the corresponding recruitment strategies are described below:

- **PPI group -** All eleven members of an OHCA research PPI group were invited by email to participate in a focus group discussion. The group had been involved in the development of this research project and showed a keen interest in participating. The PPI group also had very recent experience of participating in focus group discussions for a different PhD project examining quality of life assessment after OHCA.
- **Representatives of relevant charities -** Senior non-clinical members (for example chief executive officers) were contacted by email via charity webpages and the Association of Air Ambulances. In addition, I attended the annual conference of the Association of Air Ambulances with the initial plan to conduct a focus group during the conference. However, it became clear that I would not be able to get all of the potential participants into one room at the same time, as they did not want to miss different parts of the conference. I therefore changed strategy to one-to-one interviews during the weeks following the conference, conducted at charity offices or, in one case, in a café in London.
- **Ambulance commissioners -** A group of UK ambulance service commissioners were contacted by supervisor JB via email and, after repeated follow-up via email, agreed to arrange a focus group discussion during one of the group's regular meetings. Due to the limited numbers of ambulance commissioning forums or groups, I will not describe this group in further detail in order to maintain confidentiality.

- **Prehospital researchers -** I identified potential participants by reviewing the programme of a national scientific EMS conference. I contacted the potential participants via email and then approached them in person at the conference. I had met three of the four participants of this group in a professional capacity before, but had not worked with any of them directly. I purposefully sampled researchers from early (PhD applicant) to senior (professor) career stages (maximum variation sampling). I arranged one-to-one interviews, either in person or over the phone, in the weeks following the conference.
- **Prehospital providers -** A research paramedic from one of the participating ambulance trusts offered to arrange a focus group during the 6-weekly clinical governance meeting of regional critical care paramedics. This was set up via email and I undertook the focus group at their local ambulance station.

5.2.4 Ethics and consent

In keeping with the approval granted by the Sheffield National Research Ethics Service Committee, York and Humber on 29 July 2016 (reference number 16/YH/0300) and the research protocol, all participants were given written patient information sheets and written consent was obtained prior to the interviews; see Appendices A1 and A2.

5.2.5 Interviews/focus groups

All selected stakeholder groups were known to have previous experience in and/or an understanding of prehospital research. Prior to each focus group/interview, participants were given a short presentation on the overarching research project and the issues outlined in Section 5.1. Participants were asked if they required any further information prior to starting. This was only requested by the PPI group who considered a clear understanding of the difference between the two potential interventions (Advanced Life Support (ALS) and prehospital critical care) to be essential for the discussion. If confusion or misunderstandings arose, particularly in regards to the difference between randomised controlled and observational research, this was explained during the focus group/interview, where needed.

The duration of the focus group discussions was 45 to 90 minutes; for the interviews this was reduced to 30 to 60 minutes. All focus group discussions and interviews were undertaken in a semi-structured fashion (Koshy, Koshy and Waterman, 2010). The question guide was constructed to explore the three key questions underpinning this research, as outlined in the Section 5.1 (research priorities, randomisation and funding decisions); see Appendix A3. Each subject was introduced with an open question; follow-up questions were increasingly directed as required. Only minimal refinement of the question guide was required over the course of the research, as well as minor adjustments to accommodate each stakeholder groups' distinct background.

All focus groups and interviews were undertaken by myself and audio recorded. In addition, I took brief field notes during the focus groups/interviews. I was unable to provide a second person to facilitate the focus groups/interviews, due to not having applied for corresponding funding and the geographical spread of the interview locations. I debriefed with my supervisor after each focus group and after completion of four interviews for each stakeholder group. All recordings were transcribed using a professional transcription service.

5.2.6 Data analysis

The field notes, recordings and transcripts were analysed using the framework approach. The framework analysis was originally developed for use in large-scale policy research in the 1980s (Ritchie and Lewis, 2003), but has since been adopted and widely used in various health research settings (Gale *et al.*, 2013; Heath *et al.*, 2012). It sits within a family of qualitative analysis methods often referred to as content analysis or thematic analysis, which are based on the grounded theory approach (Chapman, Hadfield and Chapman, 2015).

The defining features of framework analysis are the systematic and structured approach to qualitative data analysis with a focus on results that can inform further action (Ritchie and Lewis, 2003). The data output frequently used is tables consisting of cases (in this project stakeholder groups) combined with pre-defined or emerging themes (Gale *et al.*, 2013). With this highly structured process and spreadsheet-like outputs, framework analysis can be mistaken for a quantitative approach to qualitative data. However, as Gale *et al.* (2013) point out in their description of framework analysis, the method does not remove the need for the researcher to make analytical decisions and explore emerging themes and relationships between themes. Likewise, reflexivity, rigour and quality of the research will need to be measured as for any other qualitative method.

I undertook the analysis with JBR regularly reviewing the findings and providing feedback. In addition, emerging themes and my interpretation of findings were cross-referenced with the impressions of the transcriber, who immersed herself in the recordings during the transcription process and took an interest in the project. Framework analysis for this project followed a five-step approach and was undertaken using N-Vivo software (version 11, QRS International); see Box 5.1.

Box 5.1. Steps of the framework analysis used for this project

1. **Coding -** I reviewed all transcripts multiple times. I used a mixture of predefined codes (deductive element), based on my previous experiences, and combined these with an open coding strategy (inductive element) to include possible unexpected but important themes.
2. **Construction of a thematic framework -** All codes were reviewed and arranged according to the three pre-determined topics (research priorities, attitudes towards randomisation and funding strategies). Within each of the three topics, codes were grouped into themes and sub-themes which emerged during the analysis, creating an initial framework.
3. **Indexing -** The framework created in step two was systematically applied to all transcripts, while paying particular attention to any data which might not fit the framework.
4. **Charting -** Data supporting the themes and sub-themes were condensed and rearranged within the framework to facilitate analysis. For each topic, this was done first by case (stakeholder group), then by theme.
5. **Mapping and interpretation -** I mapped the range and nature of themes as well as their interactions and relationships. I searched for underlying structures and explanations for the findings of the framework.

In regards to data saturation, there is only limited data on which to base an accurate estimate as some of the stakeholder groups have, to my knowledge, never been researched. Given the anticipated homogeneity of views within each stakeholder group, I anticipated that views could be explored sufficiently within one focus group or four interviews for each stakeholder group. Together with my supervisor, I assessed whether the discussions were exhaustive and/or views fully explored after each focus group or four stakeholder group interviews. If we considered further focus groups or interviews with a given stakeholder group to be of potential benefit, the protocol allowed for a further round of focus groups and/or another four interviews per stakeholder group. The decision on whether to extend data collection in this fashion was based on a consensus between myself and my supervisor, rather than predetermined criteria.

5.2.7 Data presentation

In keeping with the research questions, Section 5.3 will present the results according to the three main topics:

- Topic one - priorities influencing prehospital research
- Topic two - randomisation without consent
- Topic three - funding decision making

Presenting the results in this way will allow readers to develop a detailed understanding of each topic, which can then be applied in practice. To further aid practical application of the results, I present the findings in distinct steps. Each stakeholder group's view will be described in detail to allow a detailed understanding of how each group's unique views. This is followed by a short summary of the topic to aid comparison between the groups.

During the data analysis described in Section 5.2.6, I deliberately refrained from attempts to identify or apply existing concepts relating to the results from the focus groups/interviews. This was done to avoid the risk of the focus group/interview process to change significantly over the course of the research, due to gradual incorporation of external concepts (Creswell and Plano Clark, 2011). Once data collection was complete and themes emerged during the framework analysis, I began to search the literature for relevant concepts in a focused, non-systematic fashion. I found the following concepts to be of importance when placing the stakeholders' views in a wider context:

- Fairness or equity
- Beneficence or the Rule of Rescue
- Scientific enquiry

Section 5.3 will focus exclusively on the intrinsic research findings, in order to provide a clear description of stakeholders' views. Following this, Section 5.4 will provide a wider context and describe how the stakeholders in this research balance the values and limitations of equity, the Rule of Rescue and scientific inquiry.

5.3 Results

In total, 23 people participated in three focus group discussions and nine people participated in eight interviews (one interview with air ambulance charity representatives included two members of the same charity). See Table 5.2 for an overview of the demographics of the participants, according to stakeholder group. Appendix A4 contains illustrative sections of the transcript of the focus group with the prehospital critical care providers.

Table 5.2 Participant demographics according to stakeholder group

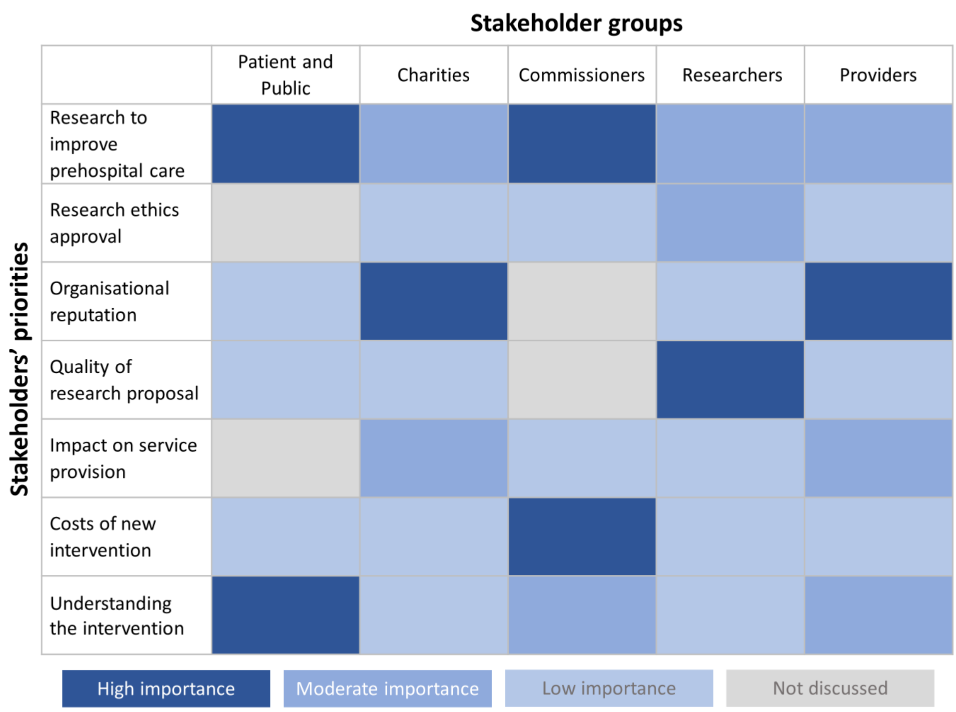
Stakeholder group	Format	Participants
Patient and public involvement	Focus group	Four female and five male Age 50s to 70s Eight participants were survivors, close friends or relatives of survivors of OHCA. One participant was previously a patient in the intensive care unit but had not suffered an OHCA. Issues of prehospital research including ethics have been discussed previously in this group.
Air Ambulance Charities	Interviews	Three female and two male Age 40s to 60s All participants were senior non-clinical staff of UK air ambulance charities. All charities represented had been involved in prehospital research before.
Ambulance commissioners	Focus group	Four female and two male Age 40s to 60s All participants were part of a national ambulance service commissioning group and regularly discuss funding of prehospital care.
Prehospital researchers	Interviews	Two female and two male Age 30s to 60s All participants had published prehospital research. Academic experience ranged from junior (PhD applicant) to senior (university professor) researcher.
Prehospital provider	Focus group	Eight male, no female Age 20s to 50s All participants were critical care paramedics. The group meets every few months for training and to discuss clinical issues.

OHCA: Out-of-hospital cardiac arrest, UK: United Kingdom

5.3.1 Topic one - priorities in prehospital research

As hypothesised, views regarding the priorities influencing prehospital research were similar within each stakeholder group, but differed significantly between groups. Figure 5.1 provides an overview of the importance of the main priorities for each stakeholder group, based on the frequency that the topic occurred, the strength of the opinions expressed, and whether participants discussed the topic spontaneously or after prompting.

Figure 5.1 Visual representation of the priorities influencing prehospital research, according to stakeholder group



Main themes:

- ***Broad support for research to improve prehospital care***
- ***Differences in stakeholders' strategies to improve prehospital care***

The PPI group focused strongly on research delivering the best possible care for individuals suffering from OHCA and making this optimised care equally available to every OHCA patient. The group members linked their desire to improve care with their own experiences of OHCA. They were also keen to gain a better understanding of how the intervention of prehospital critical care works and how it differs from the standard of ALS prehospital care. The participants considered this information important when evaluating prehospital critical care as a potential study intervention.

"So I really would like to think that what comes out of cardiac research is that what I received [prehospital critical care] becomes available nationally." (PPI group)

The representatives of air ambulance charities were all supportive of prehospital research. They saw its benefits in two possible ways: to support the current practice of air ambulances and to guide further development. Evidence showing benefit from prehospital critical care would make it easier to raise funds. Once raised, the participants felt that research could help them to spend these funds responsibly and efficiently. All participants carefully considered the risks of research participation resulting in negative media coverage and publicity. On the other hand, they also described the benefits of being publicly perceived as proactively improving care through participation in research.

"Because we exist through publicly raised funds. … if something gets out in the media, or it's presented in a way that knocks the charity's credibility or its brand, then, obviously, that could be fatal to these organisations." (Charities)

The ambulance commissioning group focused on quantifying the costs and benefits of any new intervention as the priority of prehospital research. Not surprisingly, the group expressed a strong interest in the costs of any new intervention, referencing limited budgets and a need to provide services for whole populations, rather than working at the level of individual patients. The need for cost-effectiveness is also reflected in the commissioners' desire to fully understand the intervention, which would allow them to evaluate potential modifications to the intervention in order to increase its cost-effectiveness.

"Does [prehospital critical care] give you better outcomes for sufficient numbers of patients to justify that expense?" (Commissioners)

Participants of the academic stakeholder group linked improving prehospital care through research to the provision of cost-effective and evidence-based care. The main focus of research should be to produce high quality evidence which creates the foundation of good prehospital care. The priority of research quality was further evidenced by a focus on appropriate research ethics reviews and approval as well as sufficient funding and planning of the research, in the context of existing literature.

"I think it's only worth investing in clinical care if you know that clinical care is effective. And so that's why good research and sound evidence is a prerequisite for good clinical care." (Prehospital researchers)

The group of prehospital critical care providers were keen to evaluate individual aspects of their practice through research, but expressed concerns regarding research which would scrutinise their overall effectiveness. The prehospital critical care provider group strongly considered the effects of research participation and outcomes on the reputation of their service. While funded through NHS services, the providers felt vulnerable to budget cuts which might be triggered through negative findings or complications of participation in research projects. On the other hand, participation in research resonated with the providers' concepts of professional practice.

"So I think we continually have to try and prove our worth, don't we. And then if something exposes actually, guys, you're really not needed, well, … nails in our own coffin." (Prehospital providers)

The main theme which emerged from the discussion of priorities influencing research was the consistent emphasis by all stakeholders on their support for prehospital research with the aim of improving prehospital care. While all groups agreed on the importance of improvements in prehospital care, each stakeholder group differed in their approach to this priority. Table 5.3 illustrates the sub-themes of how strategies to improve prehospital care through research are determined by the context and perspective of each stakeholder group.

Table 5.3 Context, perspective and resulting strategies of stakeholder groups

Stakeholder group	Context	Perspective	Strategy to improve prehospital care
Patient and public involvement	Personal experience of life-threatening, dramatic event and interventions	• Individual • Patients with OHCA	Optimise care for every patient with OHCA
Air ambulance charities	Relying on public funding to provide prehospital care additional to NHS care	• Regional • Patients with severe injury or illness	Support and optimise air ambulance practice
Ambulance service commissioners	Constrained budget with decision-making limited by guidelines and policy	• National • All patients receiving prehospital care	Maximise benefits to all patients within budget limits
Prehospital researchers	Discuss and analyse questions in theoretical/ hypothetical terms	• International • All patients	Create high quality research to compare a wide range of interventions
Prehospital providers	Professional identity of prehospital critical care provider	• Individual/regional • All patients treated by provider/EMS	Prove value of own practice and optimise team effectiveness

OHCA: Out-of-hospital cardiac arrest, NHS: National Health Service, EMS: Emergency Medical Services

5.3.2 Topic two: Randomisation of prehospital critical care

When considering prehospital critical care as a healthcare intervention for the condition of OHCA, the five stakeholder groups came to remarkably different conclusions regarding the ethics of randomising the delivery of such a service within the context of a clinical trial. The reason for this discrepancy can be largely explained through each group's perception of the intervention (prehospital critical care) and condition (OHCA).

Main themes:

- ***Emotive versus evidence-based considerations***
- ***Prehospital critical care as a unique healthcare intervention***
- ***Out-of-hospital cardiac arrest as a unique condition***

The PPI group strongly rejected any form of randomisation of prehospital critical care for OHCA. They perceived prehospital critical care services to be beneficial, based on their personal experiences of OHCA and a general trust in physicians delivering best care. There was concern that the level of skills of ALS paramedics was not the same as that of physicians/critical care teams and that ALS paramedics therefore might be unable to deliver the same level of care for OHCA, including the transfer of patients to cardiac centres. Another reason was the condition of OHCA itself. Patients with OHCA were perceived to be in a unique state between life and death where anything but the best attempt at restoring life was deemed unethical. The group showed a strong interest in using observational methods of research as alternatives to randomisation but struggled to clearly differentiate between randomisation in terms of research trial design and the randomness of factors determining prehospital care in practice.

" … they've had a cardiac arrest and they've gone and so the critical care team, someone brings them back to life. And therein lies my main worry. You can never have a true randomised trial. Because you are ultimately playing god." (PPI group)

The air ambulance charity representatives also strongly rejected randomisation of existing critical care services. When considering the cluster randomisation scenario, some participants supported the concept while others rejected it largely due to fund-raising concerns and a lack of equipoise. Prehospital critical care teams were perceived to provide best possible care to patients in need, thus adding value independently of clinical outcomes. Like the PPI group, charity representatives expressed interest in observational research and taking advantage of the natural experiment caused by air ambulances not always being available to attend cases of OHCA.

"I think it's very, very difficult. ... I can sort of feel that it's easier with a drug trial to randomise treatment. Because there's no proven benefit to the drug. But when you're saying that some people [pause] would get help or a service, and other people just wouldn't on a random basis, that sounds really bad." (Charities)

The ambulance commissioners acknowledged that randomising prehospital critical care would be ethically and logistically very challenging, but didn't oppose the concept on principle. Cluster randomisation was seen as generally acceptable, due to avoiding randomisation at the individual patient level. The commissioners demonstrated equipoise in relation to the potential clinical benefits of the intervention of prehospital critical care. However, they also perceived it as expensive and beneficial to only a relatively small number of patients with OHCA.

"I would go back to the question, though why would anybody be investing that level of money into [randomising] a critical care team in that way, on a hypothesis which doesn't seem to have much evidence behind it to even get that point?" (Commissioners)

In contrast to all other stakeholder groups in this study researchers strongly encouraged randomised study designs to address the question of benefit of prehospital critical care for OHCA. They acknowledged the ethical and practical challenges, but considered cluster randomisation to be a suitable solution to these. The researchers considered there to be equipoise in relation to the benefits of prehospital critical care and rejected the notion that a team of (critical care) practitioners was a fundamentally different intervention than, for example, a single drug. Likewise, OHCA was considered no different from other health states. The researchers were very sceptical about the potential of observational research to deliver reliable and accurate results, due to the inherent risks of confounding and bias. Observational research was largely seen as providing indicative information about an intervention, to generate hypotheses for subsequent testing in a randomised trial.

"Well whilst [patient-level randomisation] is not unacceptable to me, I think the best way to do it is probably at a cluster level." (Prehospital researchers)

The prehospital critical care providers were not comfortable with the idea of being randomised to attend OHCA. This did change with the suggestion of cluster randomisation, due to the idea of not reducing an existing service and randomisation not occurring on an individual patient level. The prehospital critical care providers considered their care beneficial to patients, based on their personal experiences. As prehospital critical care providers regularly deal with OHCA in their day-to-day activities, they did not consider OHCA to be significantly different from other conditions.

"Basically we're happy to randomise things that we think don't work. Aren't we. And we've got belief that we potentially do [improve outcomes]." (Prehospital providers)

The main factors which determined stakeholder groups' attitudes towards a potential randomised controlled trial and different randomisation methods were their perception of OHCA and prehospital critical care. The PPI group's and air ambulance charity representatives' argument against randomisation were based largely on emotive concerns invoked by the imminent life-or-death situation of OHCA and the perception of prehospital critical care being beneficial. Withholding a combination of advanced technology (helicopters), interventions (critical care interventions) and expertise (critical care providers) from patients who need these the most would run contrary to the mission statements that most air ambulances advertise: to be there in a time of need, and to save lives. Probably the starkest contrast to this point of view was expressed by the group of NHS ambulance service commissioners who acknowledged the emotive issues of randomisation but were mainly concerned about excessive costs of prehospital critical care. Similarly, the researchers interviewed in this study considered preconceived ideas about benefits or costs or emotive associations as largely irrelevant, unless based on reliable evidence. Finally, for the group of prehospital critical care providers, the intervention of interest was strongly linked to their professional identity and perceived expertise. Randomising prehospital critical care for OHCA was therefore seen as ethically difficult but more importantly as a gamble that might either support or threaten the providers' professional identity and future role.

5.3.3 Topic three – funding decision making

Given that a definitive randomised controlled trial of prehospital critical care for OHCA is unlikely to be feasible in current circumstances, all stakeholder groups were asked about their views on funding support for this intervention based on limited evidence. Similar to the previous two topics, opinions differed significantly between, but not within, the groups.

Main themes:

- ***Importance of research for funding decisions***
- ***Impact of factors other than research findings***

The PPI group agreed that funding decisions should not rely on randomised trials alone, but suggested optimised observational research, supplemented by common sense and social acceptability, as sufficient to guide funding decisions.

"So funding is an emotional decision. … Which will always be, regardless of whether you have a randomised set of data or observational." (PPI group)

Participants from the charity stakeholder group acknowledged the traditional hierarchy of evidence. However, given the direct commissioning of the service through public donation, charity representatives felt that public opinion and demand was a strong factor in guiding their funding decision making.

"What we require in terms of evidence is probably a lot less because we're going to be able to take that view of, well, common sense … " (Charities)

Commissioners referred to NICE guidelines and acknowledged the importance of high quality evidence, particularly the cost-effectiveness of interventions. However, scientific evidence would need to be evaluated in the context of other factors, mainly budget limitations and policy decisions made by central healthcare bodies.

"That you would look at the strength of evidence but you have to weigh that up against everything else. I.e. the cost and what're you going to compromise in terms of other services." (Commissioners)

The researchers accepted that funding decisions might have to rely on observational research on occasions. However, they strongly rejected the idea that common sense and/or emotional arguments should aid decision making. This rejection was largely justified through examples where interventions were implemented based on common sense or a perception of benefit, only to be subsequently shown to be non-beneficial or even harmful in more rigorous research. The researchers also referred to the ethical requirement of achieving optimal outcomes for a whole population in a fair manner, guided by high quality evidence.

"So if we're uncertain what to do, then doing more of what's uncertain isn't actually going to improve things for patients. And so I think that's a job for researchers to persuade people that [further] research is needed in those situations." (Prehospital researchers)

In the absence of high-quality research, the prehospital provider group suggested utilising stakeholder surveys (ALS paramedics, receiving hospitals and the public) to guide decisions about funding. Negative observational research findings regarding the benefits of prehospital critical care following OHCA could be used to optimise dispatch criteria and protocols for OHCA, rather than dismantling the service altogether.

" … this is a very multi-faceted set of interventions that we're talking about, so once we've got that initial piece of information [research findings], we can drill deeper to find out what is working and what isn't." (Prehospital providers)

When discussing the funding of prehospital care, all stakeholder groups acknowledged the importance of research findings in the decision making process. However, each stakeholder group highlighted factors specific to their background, which would also need to be considered and might even outweigh research findings when making funding decisions. The PPI group emphasised the need for social acceptability, while charity representatives considered public demand and opinion to be a significant driver of their funding strategies. Commissioners, on the other hand, acknowledged that budget limitations and policies would potentially limit the impact of research on their decision making process. The stakeholder group of researchers considered factors other than high-quality evidence to be potentially misleading and, therefore, harmful to patients. Finally, the group of prehospital providers suggested a combination of stakeholder and expert opinion as a suitable supplement to observational research in prehospital care.

5.4 Discussion

The five stakeholder groups in this research displayed divergent views of research and funding strategies in relation to the complex intervention of prehospital critical care for the life-threatening condition of OHCA. As demonstrated throughout the topics and themes presented in Section 5.3, the reasons for this divergence can largely be explained by the different personal experiences and situational contexts of each stakeholder group. Many aspects of the strategies suggested by the stakeholder groups only partially align with the principles of traditional evidence-based medicine, but are held with strong conviction. However, despite these often opposing views, a common appreciation of the concepts of scientific enquiry, fairness and beneficence can be identified, and is further discussed here. Focusing on common values rather than opposing strategies can support successful stakeholder engagement in research of complex interventions.

5.4.1 Fairness and equity

Fairness was referred to frequently by stakeholder groups during the discussion of research priorities and funding decisions, but the interpretation of this concept differed between groups.

The PPI group and charity representatives focused strongly on the provision of optimised prehospital care to patients with OHCA or critical illness, respectively. They essentially argued for vertical equity, whereby patients with the greatest need receive the most services (Panteli, Kreis and Busse, 2015). OHCA is an unpredictable, often chaotic and dramatic event with a 90% mortality rate and potential for psychological distress for survivors and witnesses (Smith *et al.*, 2015; Herlitz *et al.*, 2007). Providing a higher level of care for OHCA than for less severe prehospital conditions could be considered a fair approach, when fairness is viewed under the principle of vertical equity (Mooney, 2000). A limitation to this argument is the fact that vertical equity seeks to balance health resource distribution where outcomes are unnecessarily unfair, rather than inevitably unequal (Whitehead, 1992). The question in this context therefore is: is a 90% mortality rate from OHCA a consequence of insufficient (and unfair) resource distribution? Or is it an inevitable aspect of OHCA, despite adequate treatment?

The two stakeholder groups in this study which argued the latter, were the ambulance service commissioners and prehospital researchers. From their perspective, ambulance services already commit a significant amount of resources to the standard treatment of the relatively small number of patients with OHCA (Johnson and Sporer, 2010). Further increasing the level of care at increasing costs was perceived as unfair to other patients, in keeping with the principle of horizontal equity (Wenzl, McCuskee and Mossialos, 2015).

As patient and public involvement is an increasingly important factor in both research and healthcare commissioning. An understanding and awareness of the underlying value judgements of all stakeholders is crucial if these models of shared decision-making are to prove successful (O'Shea, Chambers and Boaz, 2017).

5.4.2 The Rule of Rescue and randomisation

Probably the most emotionally and ethically challenging aspect of this study was the discussion about randomising prehospital critical care for OHCA, with views ranging from outrage at the very idea (PPI group) to the concept being difficult but acceptable (researchers). While some of this variation can be explained by the different stakeholder perspectives of equipoise and understanding of randomisation, the Rule of Rescue also played a role in this debate (Cookson, McCabe and Tsuchiya, 2008).

The Rule of Rescue describes the human instinct to render assistance to individuals in immediate peril, irrespective of the costs and sometimes even personal risk. It was the image of experienced healthcare providers, equipped with advanced technology, standing by, while an identifiable individual was fighting for survival during OHCA, which made the randomisation of individual patients challenging for the majority of stakeholder groups. Removing either the human expert element from the intervention, or the imminent life or death struggle from the condition, eased the emotional imperative during these discussions and made randomisation largely a question of equipoise and logistics.

On the other hand, cluster-randomisation acts to move the randomisation process away from the individual and prevents the identification of a single patient in peril, making it the preferred choice of stakeholders in this study. Of note, cluster randomisation of prehospital critical care for OHCA was still considered unethical by the PPI group in this study, and significant ethical challenges, particularly in relation to individual patient rights, remain (Weijer *et al.*, 2011).

Regarding healthcare funding decisions, the National Institute for Health and Care Excellent (NICE) considered the Rule of Rescue in one of it Citizen Reports (National Institute for Health and Clinical Excellence, 2006), but explicitly did not adopt it in the guidance on social values judgement (National Institute for Health and Clinical Excellence, 2008).

5.4.3 Scientific enquiry

Despite a clearly expressed enthusiasm for, and appreciation of, the importance of prehospital research, views on the relative importance and ideal conduct of this research varied amongst stakeholder groups.

The PPI group's views on randomisation of prehospital critical care for OHCA were dominated by a perceived lack of equipoise regarding prehospital critical care and a general unease about the randomisation process during an ongoing OHCA. A systematic review found randomisation without consent in emergency research to be acceptable to about 50% of the participants included (Lecouturier *et al.*, 2008). Dickert and Kass (2009) interviewed survivors of OHCA and their relatives regarding their views on research and randomisation without consent in OHCA. In contrast to these findings, the OHCA survivors in the study by Dickert and Kass (2009) were largely supportive of randomisation. This can probably be explained by the fact that the scenarios of randomised controlled trials (RCTs) discussed in the research by Dickert and Kass (2009) involved simple drug interventions or new, unproven experimental interventions with clear equipoise. Similarly to these findings, participants in the PPI group in this thesis considered the randomisation of different advanced airway management strategies to be acceptable. In keeping with other previous findings, the PPI group participants perceived the randomisation process as risking trivialisation of significant healthcare decisions and did not always appreciate the differences between observational and experimental research designs (Robinson *et al.*, 2005; Jenkins *et al.*, 2002).

The role of charities in UK healthcare provision is likely to increase over the coming years, providing both opportunities and new challenges for medical research (Sheaff *et al.*, 2016). To the best of my knowledge, this is the first research describing the views of UK air ambulance charities on their involvement in research. It is encouraging that all charities in this study were supportive of, and involved in, research. However, the restrictions associated with fund raising requirements need to be considered in this complex setting (McCartney, 2015). Charity representatives frequently stated the aim of their research involvement as *"to* *prove what we do works*", rather than critically evaluating practice. This focus on benefits of interventions rather than lack of benefit or even harm is not unique to the charity sector but a frequent source of selection or publication bias in health research (Starks, Diehr and Curtis, 2009). This risk of bias is likely going to be more pronounced in research undertaken with charity involvement.

Perhaps unsurprisingly, the views of both the commissioners and researchers in this group largely aligned with the principles outlined in NICE's *Social Values Judgments* document, namely cost-effectiveness, fair distribution of resources across the population, and to not offer effective treatment if the costs to the population are inappropriately high (National Institute for Health and Clinical Excellence, 2008). For the commissioners in this study, these ideals competed with the imperative of achieving externally determined targets and the reality of a limited healthcare budget.

Finally, this study considered the impact of research on the intervention itself; prehospital critical care providers. Participation in research was seen as consistent with their professional identity as modern and effective healthcare providers, yet threatened this very identity if negative results ensued. This finding is consistent with previous studies of paramedic involvement in prehospital research and is an important aspect to consider (Brandling *et al.*, 2016; Watson *et al.*, 2012). For prehospital research to be successful, paramedics require a thorough understanding of evidence-based medicine and concepts such as opportunity costs which might arise from simply maintaining the status-quo of current practice (Hargreaves, Goodacre and Mortimer, 2014). To fully engage prehospital providers, prehospital researchers will need to clearly outline the need for and consequences of a proposed prehospital research project and minimise the impact on paramedics' perceived autonomy and ability to provide best possible care (Watson *et al.*, 2012).

5.5 Challenges and limitations

5.5.1 Combining focus group discussions and interviews

While the original protocol proposed focus group discussions with each stakeholder group, I had to resort to a combination of interviews and focus group discussions; see Section 5.2.2. Given the potential for the research methods to influence the results, it is worth asking if the findings for each stakeholder group would have been significantly different if focus group discussions were used instead of interviews, or vice versa.

The PPI focus group discussion was very lively and the participants certainly did not feel pressured to give answers which would please me. Further positive aspects were that the group was well established and participants were very open about their personal experiences. In addition, it was a very efficient way of recruiting participants and undertaking data collection. On the other hand, the group discussion was clearly dominated by a number of individuals with very strong opinions and personal agendas. I believe that in one-to-one interviews, some of the less dominant individuals would have had a better chance to express their opinions, which might have resulted in a more nuanced and multi-facetted picture of the PPI stakeholder group's views.

The next group were the air ambulance charity representatives, where using interviews was the only viable method of participant recruitment. The participants discussed sensitive topics such as organisational reputation quite openly and there was very little variation between them. This openness and frank honesty might not have been achieved in a focus group discussion, given that all participants worked for potentially competing organisations and may have been more guarded.

The group of ambulance commissioners all worked in different parts of the country and had busy schedules. Incorporating the focus group into their monthly meeting was therefore the most efficient strategy. The group was also accustomed to discussing difficult funding decisions and, with the focus group being conducted within their comfort zone, a good group dynamic unfolded. Views were very homogenous and it is unlikely that the findings would have changed if I had chosen individual interviews.

The next stakeholder group were researchers with a prehospital research focus. After my previous experience of failing to set up a focus group during a conference, I opted for one-to-one interviews which, for efficiency reasons, included two telephone interviews. While all researchers had broadly similar views on the topics discussed, they used slightly different arguments to justify these opinions. A focus group might have allowed me to better explore the underlying principles, if the group members had challenged and questioned each other. I could not identify any detrimental effect of conducting telephone interviews; in fact the participants seemed relaxed and comfortable when discussing more challenging issues. This was possibly helped by having met face to face prior to the telephone interview and the researchers being in their own environment.

Finally, I conducted a focus group discussion with the critical care paramedics. After an initial presentation of the background and aims of the research, the initial wariness of the paramedics gave way to a relaxed and jovial discussion amongst colleagues, with excellent group dynamics. I feel that the power relationship would have been an issue in individual interviews, and participants possibly would not have been as open (Krueger and Casey, 2015).

In summary, I do not think that the choice of focus group versus individual interviews had a significant impact on the findings presented here. Each method worked to a variable extent, depending on the characteristics of the particular stakeholder group. This is likely to be due to the strong differences between the groups, which I will further discuss in the next section.

5.5.2 Substantial differences between stakeholder groups

During the preparation phase for the research, I had prepared a topic guide to be used for all groups, which included question strategies and hypothetical scenarios to elicit certain points of view. However, it became clear very quickly during the early stages that the approaches to discussing the research topics varied so significantly between stakeholder groups, that the interview or discussion strategy would need to be adapted for each group. Probably the most challenging focus group discussion was that with the PPI group. Even carefully worded challenges of the group's strongly held convictions were met with quite emotional responses. Hypothetical scenarios designed to test underlying principles almost invariably led to discussions of the shortcomings of current prehospital and general healthcare. This was in particular contrast to the one-to-one interviews with researchers, some of whom seemed to try and avoid challenging aspects of the discussions through intellectualisation and referring to theoretical frameworks. Consequently, I adapted the question guide slightly for each stakeholder group, while maintaining the focus of the three key questions. The other three stakeholder groups were less challenging and were able to approach the questions from both personal and theoretical perspectives.

5.5.3 Are the stakeholder groups representative?

As discussed in Section 5.2.2, I used a convenience sampling strategy to recruit participants to four of the five stakeholder groups. Only for the group of prehospital researchers did I deliberately choose participants of different career stages, with the assumption that views might be affected by the amount of previous research experience. This raises the question of how representative the participants of the four other stakeholder group are.

Starting with the ambulance service commissioners, participants came from different parts of the country, their backgrounds were varied and included paramedics and pharmacists, and gender was well distributed. Likewise, I recruited air ambulance charity representatives from four different organisations with a good geographical distribution.

The group of prehospital providers on the other hand were all male and worked within the same organisation. The financial pressures within the organisation and the resulting drive for cost-reduction was a recurrent theme in the discussion. This is unlikely to be fully generalisable to providers working under different circumstances. However, the main findings from this group (importance of professional identity) was also identified in previous research (Brandling *et al.*, 2016) and mirrored views expressed informally by my local prehospital colleagues.

Finally, I described in Section 5.3.1 how the PPI group's view was clearly significantly influenced by their personal experience of OHCA. While their views described here are likely to be representative of other OHCA survivors and their relatives, they probably do not represent the views of the general population, many of whom will never have thought about the question of varying levels of prehospital care for OHCA. Given the definition of a stakeholder as *"a person with an interest or concern in something ... "* (English Oxford Living Dictionaries, 2017c), I would argue that the general population may not qualify as a relevant stakeholder in the context of this research question. The issue of representativeness in PPI is not a new consideration (O'Shea, Chambers and Boaz, 2017). Interestingly, the PPI group in this research showed awareness of the issue and also the problems researchers would face if trying to involve the general public, as the following quote from the PPI focus group discussion shows:

"What you say about we're sat here, we all got bias. If you were to go down into [city centre] now, and approach different people with different ages, and say if you or somebody you loved had a [cardiac arrest], would you want the best expert ambulance people, put it in lay terms, to come to you?"

"Absolutely."

"Would anyone say no?"

"Most people would say I'm not quite sure what you're on about."

[laughter]

(PPI group)

5.5.4 Researcher bias

As with all qualitative research, the results and analysis presented needs to be reviewed within the context of the researcher's background, bias and worldview. Emergency medicine as a specialty attracts a certain type of physician: being pragmatic, focused and nonjudgmental are commonly cited prerequisites for a successful career in this demanding speciality (Koyfman and Long, 2017). In Section 5.2, I described how a pragmatic approach shaped participant selection and data collection for this qualitative phase of the research.

When taking a patient's history in the emergency department, in order to come to a diagnosis or to generate a management plan, an important process is to separate signal from noise, to focus on the key features which will lead to correct conclusions, while avoiding distractions from irrelevant information (Xu *et al.*, 2012). In order to achieve this focus, we constantly make decisions on how much weight to attribute to individual pieces of information and how to structure it. Pitfalls to avoid are entering the consultation with preconceived ideas or being overwhelmed by the breadth of information provided.

When I analysed the transcripts of the interviews and discussions, I found myself following the routine I have practiced over and over again in the emergency department. I deliberately did not research any concepts, such as the Rule of Rescue or vertical vs. horizontal equity, prior to completing the analysis. During the coding and mapping process, I continuously narrowed down the focus of inquiry and structured the few key points into the themes described above. As a result, workable themes and structures are presented, at the cost of compression of the richness of the source data.

Finally, emergency physicians constantly witness humanity's dark side, with aggression, self-destruction, addiction and abuse encountered daily (Korcha *et al.*, 2014). One way to avoid arrogance and cynicism towards these often difficult patients is to adopt a deterministic worldview (Bear and Knobe, 2016). Most people probably would not actively choose a life of crime, intravenous drug use and recurrent emergency department presentations. More likely, the only differences between them and me are loving parents, lack of childhood trauma, a teacher saying the right thing at the right time, or simply fortunate circumstances. This deterministic world view, shaped and anchored by hours of providing emergency care, has significantly influenced analysis of this qualitative research. The reason I have not considered one stakeholder group's view to be more valid than another is the underlying assumption that the views are largely determined by the context and personal and professional experience of the stakeholder, rather than freely and independently formed through intellectual deliberation.

5.6 Conclusions

In this chapter, I explored the views of five relevant stakeholder groups (patient and public; charities; commissioners; researchers; prehospital providers) on research and funding of prehospital critical care for OHCA. I described how, despite the common appreciation of the concepts of scientific enquiry, fairness and beneficence, the groups displayed significantly divergent views, particularly in regards to randomisation and funding strategies. The reasons for this divergence can largely be explained through the different personal experiences and situational contexts of each stakeholder group. Many aspects of the strategies suggested by the stakeholder groups only partially align with the principles of traditional evidence-based medicine, but are held with strong convictions. While the subject of prehospital critical care and OHCA is quite specific, the concepts and themes described will also apply to other areas of medicine, particularly in prehospital or emergency care.

5.7 What next?

Following the completion of the systematic review, the qualitative research was the next phase of the PhD project to be completed. Still outstanding at this point are the observational research analysing the impact of prehospital critical care on survival following OHCA as well as the impact of discrete critical care interventions, and the accompanying cost analysis. The results presented in this chapter therefore provide context, challenges and opportunities for the following quantitative work.

The context in which this research is undertaken is far from the current ideal approach to the evidence-based introduction of healthcare interventions. In the ideal model, a new intervention shows promise in early studies and is rigorously tested in randomised-controlled trials, whilst cost-effectiveness is assessed in accompanying economic analyses. Finally, funding decisions are made based on the information provided from this research. In contrast, prehospital critical care is already well established in some but not all parts of the country. It is a complex intervention and in the absence of clear evidence, numerous stakeholders have developed strong and often emotional views about its merits.

One question I asked at every discussion was what stakeholders would do with the results of my observational research, which will show that critical care either improves or doesn’t improve survival following OHCA? The replies from many of the stakeholders made it clear that their views were not going to shift significantly with opposing research findings. The challenge which this phase of the PhD poses for the rest of the project is therefore: what good is the research if it does not change opinions? I struggled with the answer to this question initially, but finally found an answer in the concept of the Justified True Belief discussed in Chapter 3. With the true effect of prehospital critical care for OHCA impossible to ascertain, and the current lack of supporting evidence, stakeholders' only choice in this matter is to have opinions. My research, limited in its validity by the observational design, will not provide a definite answer to the research question or completely shift any of the stakeholders' views. It will, however, act to shift the focus of discussion in this area away from beliefs and towards justification, thus taking us one step closer to this particular definition of knowledge.

On the other hand, despite the often overriding interests of specific stakeholders, each group unequivocally endorsed my research project and prehospital research in general, as evidenced by their participation in this work and their expressions of support during the discussions. I was also able to review the plans for the quantitative and economic analysis in the light of the stakeholders' views. Similarly to the findings from the systematic review (Chapter 4), the stakeholder discussions presented in this chapter again emphasised the need to better understand what prehospital critical care for OHCA actually entails. This is reflected in Chapter 2, Objective 3 "t*o understand what interventions are being delivered by prehospital critical care practitioners during the care for out-of-hospital cardiac arrest."* In regards to the economic analysis, considerations of equity in prehospital care for OHCA raised the question of how much is spent on current (ALS paramedic) care and whether it is enough, too little or too much. While the initial focus of the economic analysis was mainly the incremental cost incurred by prehospital critical care for OHCA, the stakeholder discussions made me broaden this focus to investigate the current costs of ALS care for OHCA in more detail, and this is considered further in Chapter 6.

Having described the context, stakeholders' views and the underlying moral and ethical principles in this chapter, I will now focus on the quantitative and economic analysis of prehospital critical care for OHCA. These subject areas both contain their own challenges and opportunities, as the conversation between a participant and myself at the end of an interviews suggests.

“Mm. That’s the thing about what you're doing [research], it isn’t always going to give you a very clear outcome. But I don’t think that should stop you asking the question.”

“ Yeah. I'm going to turn it [the recorder] off.”

[RECORDING ENDS]

6. Original research: an estimation of the cost-effectiveness of Advanced Life Support and prehospital critical care for out-of-hospital cardiac arrest

6.1 Introduction

As demonstrated in Chapter 1, survival following out-of-hospital cardiac arrest (OHCA) depends on a number of sequential healthcare interventions, which can be summarised in the Chain of Survival (see Figure 1.7). The key interventions of the Chain of Survival are early recognition of OHCA with timely dispatch of prehospital providers, bystander cardiopulmonary resuscitation (CPR), defibrillation and optimised post-resuscitation care once return of spontaneous circulation (ROSC) has been achieved.

The first three links of the Chain of Survival are provided by bystanders and prehospital providers trained in Basic or Advanced Life Support (BLS and ALS, respectively) and are unlikely to be influenced by prehospital critical care, which tends to be a second or third tier response to OHCA (von Vopelius-Feldt, Brandling and Benger, 2017).

Prehospital critical care might improve survival by strengthening the fourth link of the Chain of Survival. However, concerns about the associated costs have been raised in previous research (von Vopelius-Feldt and Benger, 2014a; Mackenzie *et al.*, 2009), as well as in the qualitative work presented in Chapter 5. The other links in the Chain of Survival, bystander CPR and early defibrillation, seem intuitively inexpensive when compared to the costs of a highly trained team of providers, particularly if these costs include the use of a helicopter.

While evidence for prehospital critical care following OHCA is limited to a small number of observational studies (Chapter 4), bystander CPR and early defibrillation have both been extensively studied and have been consistently shown to significantly improve survival following OHCA (Perkins *et al.*, 2015b). Given the uncertainty around clinical benefit and costs of prehospital critical care, an economic analysis is required for decision makers to assess the likelihood of cost-effectiveness of this intervention for OHCA.

Furthermore, the qualitative research presented in Chapter 5 showed a discrepancy in opinion as to whether ambulance trusts in the United Kingdom (UK) and the National Health Service (NHS) spend too much or too little on the care of OHCA patients. The two questions that this chapter will therefore attempt to answer are:

- What is the estimated cost of OHCA treatment in the UK, from prehospital care to post-discharge costs?
- What is the estimated cost-effectiveness of prehospital critical care for OHCA at various hypothetical levels of clinical effectiveness?

Answering the first question will provide clarity not just about whether OHCA receives more or less resources than other conditions, but also where the costs originate along the care pathway. Determining the costs of prehospital critical care will allow me to define a minimally economically important difference in survival rates following OHCA which prehospital critical care has to achieve in order to be cost-effective. The concept of the minimally economically important difference is based on the idea that, for a healthcare intervention with known costs, a threshold of minimal clinical effectiveness can be defined, above which the intervention becomes cost-effective (Delgado *et al.*, 2013). This information will then be used to assess the adequacy of the sample size achieved in the analysis of the effects of prehospital critical care on survival, presented in the following chapter.

I described the current lack of research into the costs of prehospital critical care in Chapter 1. Economic analyses of prehospital care in general are rare, including prehospital care for OHCA. A systematic review by Lerner *et al.* (2006) identified only 32 publications examining costs of prehospital care, of which only 14 addressed costs and consequences of different treatment options. See Table 6.1 for an overview of publications in the systematic review by Lerner *et al.* (2006) which address prehospital care for OHCA.

Table 6.1 Key features of publications included by Lerner *et al.* (2006), which address prehospital interventions for out-of-hospital cardiac arrest (all compared to current EMS practice in the study areas)

Publications	**Intervention (compared to current EMS in the study region)**	**Incremental cost-effectiveness range in US Dollar per survival to hospital discharge**
Ornato *et al.* (1988) Jakobsson *et al.* (1987)	Basic Life Support providers	2,800 - 12,900
Hallstrom, Eisenberg and Bergner (1981) Nichol *et al.* (1998) Jermyn (2000) Forrer *et al.* (2002) Nichol *et al.* (2003)	Defibrillation (by prehospital providers, police, fire service or lay-persons)	7,800 - 190,000
Nichol *et al.* (1996)	Reducing EMS response time for OHCA	262,700 - 1,134,400
Urban, Bergner and Eisenberg (1981) Valenzuela *et al.* (1990)	Advanced Life Support providers	91,900 - 181,000

EMS: Emergency Medical Services, OHCA: Out-of-hospital cardiac arrest

Major limitations of the studies summarised in Table 6.1. are that they originate largely from the US or Scandinavia and the fact that most of the publications only include the costs of training providers or lay-persons, costs to EMS systems and/or early hospital costs (Lerner *et al.*, 2006). Differences in research methods as well as the large time periods between individual studies probably explain the considerable variations in cost estimates seen in Table 6.1. In addition, all of the interventions studied have since been implemented into UK EMS practice (von Vopelius-Feldt and Benger, 2014b), while in-hospital treatment of OHCA patients has seen significant improvements in post-resuscitation care (Girotra, Chan and Bradley, 2015). The economic analysis presented in this chapter will draw on the most recent and most relevant available evidence, with the aim of assessing the probability of cost-effectiveness of prehospital critical care following OHCA and estimating overall healthcare spending on OHCA.

6.2 Methods

6.2.1 Developing the protocol

The most reliable way of undertaking an economic analysis of a healthcare intervention is arguably to embed it into a randomised controlled trial (RCT) (Gray *et al.*, 2011). The elimination or at least reduction of bias and confounding through randomisation allows for a more robust estimate of the effects of an intervention on the outcome studied (Concato, Shah and Horwitz, 2000). At the same time, access to prospectively collected, patient-level costing data makes the estimate of costs associated with the intervention reliable (National Institute for Health and Care Excellence, 2013).

The observational study design I used to examine the effects of prehospital critical care on survival following OHCA did not allow me to collect treatment costs or outcomes at an individual patient level. The initial plan at the outset of the PhD was therefore to use a combination of micro- and macro-costing of prehospital critical care for OHCA, focusing on EMS systems' costs only. Results would be presented utilising a cost-consequence framework, where the costs and effects of the intervention are described separately. This approach acknowledged the limitations of the observational research design. However, its usefulness would have been limited by the exclusive focus on prehospital costs, the need for the reader to interpret costs and effects independently and the lack of comparability with other healthcare interventions (Gray *et al.*, 2011).

A major change from the initial protocol was therefore the switch to decision analysis modelling, which allowed me to include mid- to long-term costs and effects of prehospital critical care following OHCA. The change of methods was a result of further reading over the course of the PhD, in particular the book *Applied Methods of Cost-effectiveness Analysis in Health Care* by Gray *et al.* (2011), and consultation with my supervision team (JP in particular).

6.2.2 Decision analysis

Decision analysis has been used in different settings such as marketing, law and engineering, but is also increasingly and successfully used in the evaluation of healthcare interventions (Gray *et al.*, 2011). Decision analysis allows health economists to examine the costs and effects of theoretical choices made about a healthcare interventions, without the corresponding (and potentially negative) consequences occurring in the real world. Data to inform such theoretical decision models can be included from a variety of sources, and a number of alternative choices and their consequences can be modelled. As most research data includes a degree of uncertainty (usually expressed in confidence intervals or interquartile ranges), decision analysis models can include ranges of costs and effects of an intervention in the analysis. This leads to a more realistic overall estimate of cost-effectiveness.

Decision tree models are frequently used in one or more of the following circumstances alongside studies of clinical effects; adapted from Gray *et al.* (2011):

- An RCT of the intervention of interest is not feasible.
- The research does not compare all the relevant alternatives.
- Information from an number of studies has to be combined.
- The study does not include relevant long-term outcomes.

As prehospital research is frequently subject to barriers and limitations, combining evidence from multiple sources in a decision analysis model can be seen as a pragmatic and goal-oriented approach (Sun and Faunce, 2008).

In the context of prehospital critical care for OHCA, funding decisions have been made, and continue to be made, across the UK by NHS ambulance services and air ambulance charities (von Vopelius-Feldt and Benger, 2014a; Hyde *et al.*, 2012). In Chapter 5, I described how a lack of data on the cost-effectiveness of prehospital critical care for OHCA results in stakeholders' opposing views on funding such services. It is worth stating explicitly that continuing the status-quo of funding or not funding a service due to a current lack of evidence (rather than evidenced lack of benefit) are both decisions of potential magnitude and associated opportunity costs (Gray *et al.*, 2011). Any evidence to guide these decisions is therefore of great value. The aim of the decision modelling analysis is to provide stakeholders in prehospital critical care with an estimation of its cost-effectiveness following OHCA, acknowledging the uncertainty of this estimation, while drawing from the best available evidence.

Decision modelling is one of many approaches available to health economists and possesses distinct advantages and limitations which need to be considered in the planning, execution and interpretation of the economic analysis (Gray *et al.*, 2011). The main advantage in regards to this thesis is the pragmatic approach of utilising a number of potential sources of data to support the analysis, as described in Box 6.1.

Box 6.1. Steps of decision analysis modelling, adapted from Philips *et al.* (2006) and Briggs, Claxton and Sculpher (2006)

Step 1 – Define the question to be addressed by the economic analysis.

This includes the clinical setting, the range of alternatives being examined and the time horizon and perspective of the economic analysis. The boundaries of the model need to be clearly specified.

Step 2 - Select the appropriate analytical model.
The most common models used in health economics are the decision tree model and Markov model, other options include individual sampling model, systems dynamic model or discrete event simulation.

Step 3 – Create the model structure.
The model structure should include all relevant clinical events, effects of interventions and outcomes. Trade-off decisions between complex and pragmatic modelling are frequently required.

Step 4 – Identify and synthesise relevant evidence.
Potential sources are own research data, previous published studies or meta-analyses. This can be supplemented by reports from governments or other institutions. The Office of National Statistics' Life Tables (Office for National Statistics, 2016) or Department of Health's reference costs (Department of Health, 2016a) are frequently used in economic analyses the UK. If expert opinion is utilised, this needs to be clearly stated.

Step 5 – Refine and critically review the model.
The model might need to be adjusted in order to reflect and incorporate evidence identified during the previous step. Consideration should be given to external and internal validity of the model.

Step 6 – Fit parameter values and distributions.
Estimates and distributions for each parameters, informed by the data synthesis in Step 4, are fitted to the model. Care should be taken to consider appropriate distributions for different types of parameters.

Step 7 – Run a probabalistic sensitivity analysis and relevant one-way sensitivity analyses.
To reflect the uncertainty in the underlying data and to asess its impact on the estimate of cost-effectiveness of the intervention, probabalistic sensitivity analysis is undertaken. Parameters of particular interest to decision makers can be manipulated directly and assessed in more detail through a focused sensitivity analysis.

Step 8 – Present the results of the decision modelling analysis.
Results can be displayed in a variety of ways. Commonly used are incremental cost-effectiveness ratios (ICERs), the cost-effectiveness plane or cost-effectiveness acceptability curves (CEACs).

On the other hand, decision analysis modelling can be criticised for being a theoretical construct of reality, with potentially significant limitations as to how accurately the real world is reflected in the model (Briggs, Claxton and Sculpher, 2006). It is therefore important that the process of decision modelling is explicit and described in a transparent and logical manner, which I will attempt in the following sections. Particular focus will be placed on the process of information synthesis. To create the most accurate model, I will draw on my own research but also various other sources of published data.

Finally, a strength of decision analysis is the ability to reflect the uncertainty of the data on which the model was built. This will be achieved through a probabilistic sensitivity analysis, where each parameter in the model is not only assigned a single estimate value but its value is drawn from a distribution of possible values. A Monte Carlo simulation will draw random values for all parameters in the model during repeated analysis of the modelled intervention's costs and effects. The result will be a probability of cost-effectiveness of prehospital critical care for various willingness-to-pay thresholds. The decision analysis modelling in this chapter was undertaken following a step-wise approach adapted from Briggs, Claxton and Sculpher (2006) and Philips *et al.* (2006); see Box 6.1.

6.2.3 Definition of the research question

6.2.3.1 Clinical setting – Prehospital Critical Care Service 1 and Ambulance Trust Alpha

The economic analysis was undertaken in a section of a participating ambulance trust (Trust Alpha) which is covered by Prehospital Critical Care Service 1 (PCC-1). The section of Trust Alpha covers an area of 2.930 square miles with a population of approximately 2.5 million people [Trust Alpha, 2016]. The area is largely suburban or rural but has one metropolitan area and two urban areas with populations of approximately 1,000,000, 150,000 and 150,000, respectively. The overall population density is 860/square mile (UK mean 702/square mile) (Wikipedia, 2017).

6.2.3.2 Alternative interventions – Advanced Life Support and prehospital critical care

Trust Alpha provides ALS paramedic care using a combination of first responders, rapid response vehicles (RRVs) and ambulances [Trust Alpha, 2016]. The section of Trust Alpha operates 27 ambulance stations with a total of approximately 800 ALS paramedics (employed part- or full-time) as well as emergency care assistants (ECAs) and ambulance technicians (data provided by Trust Alpha). The median response time for OHCA during the study period was 7.4 minutes (IQR 4.9 minutes to 11.4 minutes) and care on scene was provided by a mean of 2.43 core resources (paramedic-staffed double-crewed ambulances and/or rapid response vehicles).

6.2.3.3 Perspective

In keeping with the recommendations of the National Institute for Health and Care Excellence (NICE), the perspective on costs chosen for this economic evaluation was that of the National Health Service (NHS) and personal social services (PSS) (National Institute for Health and Care Excellence, 2013). The perspective on outcomes included all direct health effects on patients, namely length and quality of life. When estimating whether prehospital critical care and/or ALS for OHCA are cost-effective interventions, I will use the concept of the willingness-to-pay (WTP) threshold. The concept of WTPs, their ethical implications and what value they should take are discussed in detail in Chapter 9. For the purpose of this chapter, the WTP threshold is the amount of resources (money) which a healthcare funder is prepared to spend for a defined benefit (quality-adjusted life years, QALYs). Interventions which fall below the WTP threshold are considered cost-effective. While NICE does not stipulate a definite WTP threshold, a WTP threshold of £20,000 per QALY is generally acknowledged and therefore used as the primary cut-off in this analysis (National Institute for Health and Care Excellence, 2013).

6.2.3.4 Time horizon

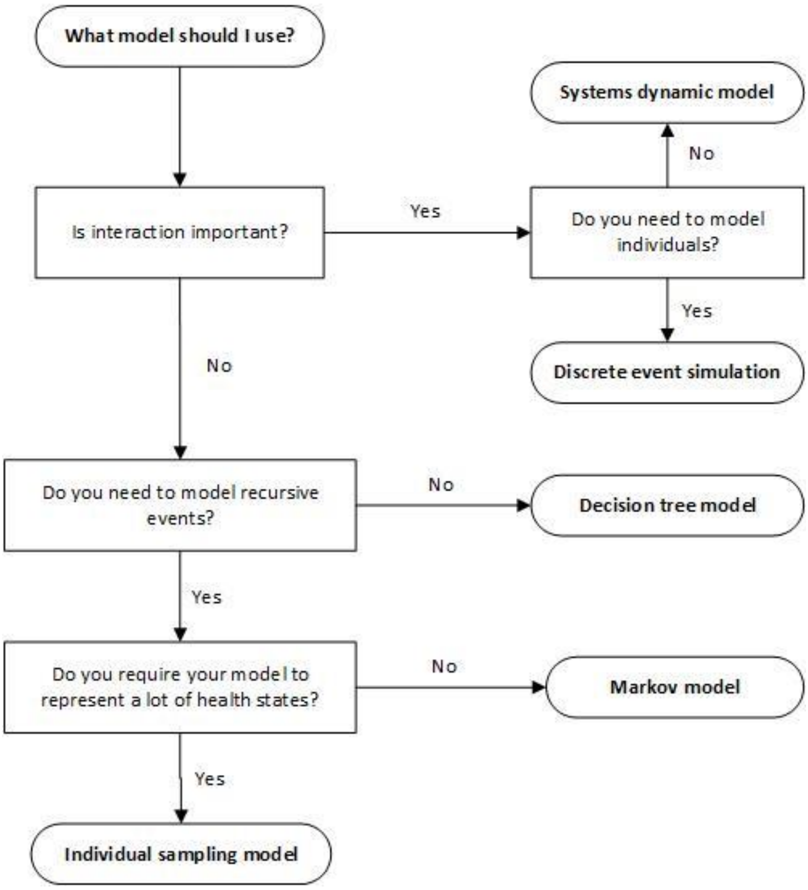
NICE states that the time horizon should be *"long enough to reflect all important differences in costs or outcomes between the technologies being compared"* (National Institute for Health and Care Excellence, 2013, *p.32).* The original protocol defined the time horizon limit at survival to hospital discharge, in keeping with the primary endpoint of the quantitative research described in Chapter 7 and national ambulance service targets (Association of Ambulance Chief Executives, 2017).

However, during the review of relevant literature, it became clear that a significant proportion of costs will occur in survivors of OHCA after they have been discharged from hospital; see Section 6.2.6 (Gates *et al.*, 2017). In addition, the qualitative research in Chapter 5 showed a clear difference in stakeholders' views of whether overall NHS spending on OHCA is sufficient. Including only prehospital and in-hospital costs would make NHS and PSS funding of OHCA care seem less than it actually is. While the focus of this economic analysis remains on prehospital care for OHCA, I have extended the time horizon to include long-term survival; see Section 6.2.7.

6.2.4 Selection of the appropriate model for analysis

When selecting the appropriate model for the decision analysis, a few important questions need to be considered. Following the flowchart in Figure 6.1, I selected a decision tree as the most appropriate model to examine cost-effectiveness of prehospital critical care following OHCA.

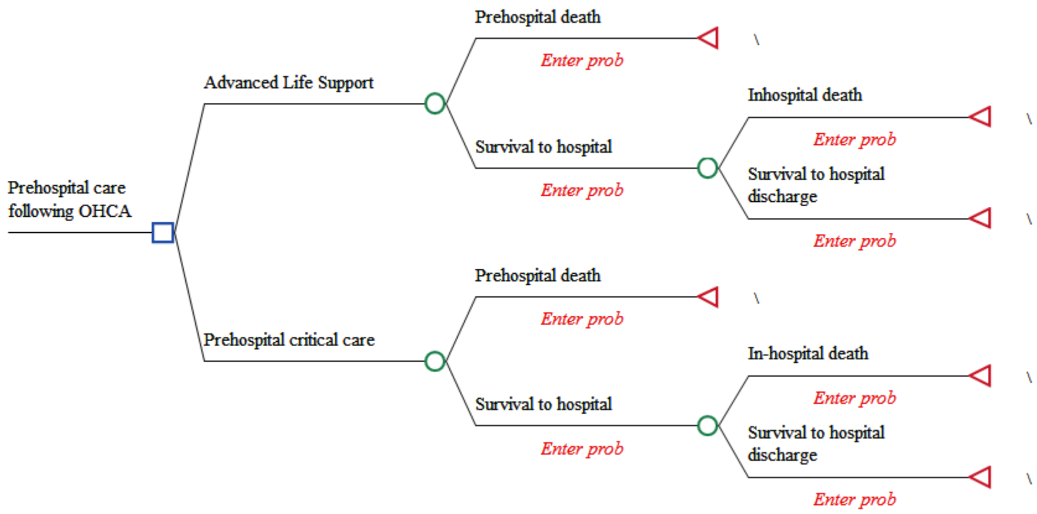
Figure 6.1 Selecting the appropriate model type, adapted from Barton, Bryan and Robinson (2004) and Gray *et al.* (2011), with permission from SAGE Publications



6.2.5 Structure of the decision tree model

The decision under investigation is the funding of a prehospital critical care service for patients suffering OHCA, when compared to the alternative of ALS paramedic care delivered by the ambulance service. The decision tree model in Figure 6.2 therefore commences with a decision node, followed by the two options under consideration, prehospital critical care or ALS care. Clinically important prehospital outcomes following either care pathway are prehospital death or arrival at hospital with ROSC. Following hospital admission, patients either survive to hospital discharge or die in hospital. Having created an initial decision tree structure, the next step is to identify and synthesise information which will allow the model to be populated with probabilities for each chance node (round nodes), as well as costs and effects for each end point (triangular nodes) in Figure 6.2.

Figure 6.2 Initial decision tree model of prehospital critical care and Advanced Life Support following out-of-hospital cardiac arrest



6.2.6 Identification and synthesis of evidence

This section provides a detailed overview of the process of identifying and selecting the data which will support the final decision tree model used in this analysis (Figure 6.6, Section 6.2.7). This includes data on costs and effects of ALS and prehospital care for OHCA in the prehospital care phase as well as in-hospital and post-discharge costs and effects. The result of this process will be summarised in Table 6.4, Section 6.2.8).

6.2.6.1 Prehospital treatment costs – Advanced Life Support

Cost data were obtained for the corresponding section of Trust Alpha, for the financial year 2015/16. The Excel spreadsheet provided by the Trust Alpha finance department included pay for clinical and non-clinical staff as well as costs of dispatch infrastructure, ambulance stations, vehicles, fuel, medical supplies, communications equipment, community first responders and third-party costs. The amount of funding spent on ALS care for OHCA was calculated as the number of OHCA cases multiplied by the number of core resources (paramedic-staffed vehicles), divided by the product of the number of cases of any aetiology and the number of core resources attending these. This was calculated from a one-year summary of the corresponding section of Trust Alpha (April 2016 to March 2017). Calculating the proportion of resources spent on OHCA in this fashion distributes the costs of waiting time of resources in between emergency proportionally between OHCA cases and those of other aetiology (Lerner *et al.*, 2012).

6.2.6.2 Prehospital treatment costs – prehospital critical care

Cost data were obtained for PCC-1, for the financial year 2015/16 in an excel spreadsheet. This included costs of the helicopter, hangar and staff area, pay for physicians and spending on training and equipment. Additional costs of two rapid response vehicles and pay for critical care paramedics was provided by Trust Alpha and calculated from the Trust Alpha data source. The proportion of PCC-1 funding spent on prehospital critical care was calculated as the number of OHCA cases attended by the critical care service, divided by number of all cases attended by PCC-1. As the vast majority of patients attended by PCC-1 are critically ill and require similar amounts of PCC-1 resources, no further adjustments between OHCA cases and non-OHCA cases was made. This was calculated from the PCC-1 clinical database for the year 2016.

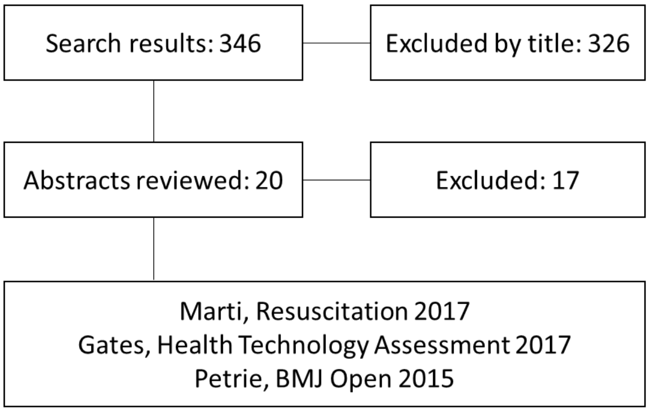
6.2.6.3 Prehospital outcomes

Outcomes of prehospital resuscitation in the ALS and ALS plus prehospital critical care group were simulated for this chapter. I ran the decision analysis model with different effect sizes of prehospital critical care when compared to ALS, with absolute differences in survival following OHCA ranging from 0% to 6%. The rate of survival to hospital arrival for the ALS group is based on preliminary data and a recent publication from the Out-of-Hospital Cardiac Arrest Outcomes (OHCAO) Registry (Hawkes *et al.,* 2017) and is set at 25.0%. Once the results of the observational research, presented in Chapter 7, are available, I will revisit the decision analysis model and calculate a further estimate of cost-effectiveness based on the best available data.

6.2.6.4 Hospital treatment costs

The costs of in-hospital treatment were based on a combination and synthesis of relevant publications, identified by a focused systematic search of the recent literature. PubMed was searched using the search string *(((cost) OR economics) OR expenditure) AND "cardiac arrest"*, with search results limited to the last 10 years. Inclusion criteria were cost analysis of any intervention in adult, non-traumatic OHCA in the UK. See Figure 6.3 for a flow chart of the search results.

Figure 6.3 Flow chart of selection of publications, search results from PubMed on 22 November 2017



Twelve of the publications for which abstracts were reviewed were excluded as they were undertaken outside the UK and were therefore likely to have significantly different cost and clinical parameters. The other five excluded studies did not include relevant costs.

Of the three full-text publications reviewed, the studies by Marti *et al.* (2017) and Gates *et al.* (2017) related to the same randomised controlled trial of a mechanical chest compression device. Hospital treatment cost estimates were based on the length of stay of patients on intensive care units (ICUs) and on regular hospital wards as well as Emergency Department (ED) and outpatient costs. In contrast, Petrie *et al.* (2015a) included significant additional costs of cardiac interventions, such as percutaneous coronary intervention (PCI), pacemaker insertion or coronary artery bypass graft surgery (CABG), resulting in a higher estimate of hospital costs for OHCA that is more likely to be accurate. See Figure 6.4 for an overview of patient characteristics, cardiac interventions and ICU support in Petrie *et al.* (2015a).

Figure 6.4 Overview of characteristics and interventions for patients admitted to ICU after OHCA in the economic analysis by Petrie *et al.* (2015a), with permission from BMJ Open (license number 4252320390390)

Patient characteristics	
Age	63.5±14.7
Male sex	50/69 (72%)
VF/VT as initial rhythm	50/69 (72%)
Bystander CPR	36/69 (52%)
Cardiac interventions	
Angiography (<24 h from admission)	48/69 (70%)
Angiography (>24 h from admission)	4/69 (6%)
PCI at initial angiography	34/48 (71%)
Repeat interventions (2 or more)	6/69 (9%)
Therapeutic hypothermia	64/69 (93%)
IABP (Intra-aortic balloon pump)	21/69 (30%)
AICD (inserted before hospital discharge)	6/69 (9%)
Causes of cardiac arrest	
Cardiac cause	54/69 (78%)
Respiratory arrest	5/69 (7%)
Pulmonary embolus	2/69 (3%)
Alcohol intoxication	2/69 (3%)
Epileptic seizure	1/69 (1%)
Electrolyte disturbance	1/69 (1%)
Cerebrovascular accident	1/69 (1%)
Unknown	3/69 (4%)
ICU Support	
Ventilation	68/69 (99%)
Inotropes and pressors	60/69 (87%)
RRT	9/69 (13%)
Tracheostomy	15/69 (22%)
Tracheostomy at ICU discharge	4/41 (10%)

AICD, automatic implantable cardioverter defibrillator; CPR, cardiopulmonary resuscitation; ICU, intensive care unit; PCI, primary coronary intervention; RRT, renal replacement therapy; VF/VT, ventricular fibrillation-ventricular tachycardia.

I used the data from Petrie *et al.* (2015a), including the study's open access source data (Petrie *et al.*, 2015b) in combination with the *Department of Health NHS Reference Costs 2015-16* (Department of Health, 2016a) to estimate the costs of in-hospital treatment. Table 6.2 gives an overview of the sources and values of the different hospital treatment costs.

Table 6.2 Summary of in-hospital treatment costs following out-of-hospital cardiac arrest

Cost group	Source used	Value in £	Variability	Financial year
ED costs per patient	Department of Health (2016a)	**372**	270-446 (IQR)	2015-16
ICU costs per day (survivors to hospital discharge)	Petrie *et al.* (2015b)	**1,668**	267 (SD)	2011-12
ICU costs per day (non-survivors)	Petrie *et al.* (2015b)	**1,690**	307 (SD)	2011-12
Non-ICU costs (per survivor to hospital discharge)	Petrie *et al.* (2015b)	**12,257**	8,033 (SD)	2011-12
Non-ICU costs (per non-survivor)	Petrie *et al.* (2015b)	**3,666**	2,410 (SD)	2011-12

ED: Emergency department, ICU: Intensive care unit

6.2.6.5 Hospital outcomes

The observational data which will be presented in Chapter 7 are limited to the outcome of survival to hospital discharge or in-hospital death. This is reflected in the initial decision tree model in Figure 6.2. However, in-hospital costs of OHCA treatment vary significantly depending on the length of stay and patient destinations within the hospital, as described in the bullet points below. The decision tree model was therefore updated to accurately reflect these different clinical pathways and their associated costs and effects; see Figure 6.6 for the final decision tree model used for analysis.

- **Death in the ED** - This is a significant pathway, as it does not incur any further costs beyond the ED, particularly ICU costs, which comprise approximately 65-75% of all in-hospital costs (Petrie *et al.*, 2015a). In a randomised controlled pilot study of 615 patients with OHCA undertaken in the UK setting in 2015, death in the ED occurred in 67 out of 190 (35%) of patients who had ROSC on arrival at hospital (Benger *et al.*, 2016).
- **ICU admission with in-hospital death -** In 2014, this occurred in 2,687 of 4,517 patients (60.3%) who were admitted to ICU following OHCA, according to data from the Intensive Care National Audit and Research Centre (ICNARC) Case Mix Programme Database analysed by Nolan *et al.* (2016). The median length of ICU stay in this group was 2.0 days (IQR 0.7 to 4.5). Using the calculations proposed by Wan

et al. (2014), the estimated mean and standard deviation of ICU length of stay are 2.4 days (2.8).

- **ICU admission followed by survival to hospital discharge -** In the 2014 ICNARC cohort, this occurred in 1,830 of 4,517 patients, with a median length of stay on ICU of 4.7 days (2.3 to 10.0), corresponding to a mean and standard deviation of 5.7 days (5.7) (Nolan et al., 2016; Wan et al., 2014).

I ran the decision analysis model with different effect sizes of prehospital critical care when compared to ALS, with absolute differences in survival following OHCA ranging from 0% to 6%. The rate of survival to hospital discharge for the ALS group was based on preliminary data and set at 9.0%. Once the results of the observational research, presented in Chapter 7, are available, I will revisit the decision analysis model and calculate a revised estimate of cost-effectiveness based on the best available data.

6.2.6.6 Post-discharge costs

In their economic analysis of mechanical chest compression during OHCA, Gates *et al.* (2017) provide a detailed assessment of post hospital discharge costs from a healthcare provider (NHS) perspective. This includes costs of hospital outpatient appointments, ED or GP visits, various rehabilitation and support services and nursing/residential home costs. Importantly, they found a significant difference between the costs incurred by OHCA survivors with good neurological function (Cerebral Performance Category, CPC 1 and 2) and those with poor neurological function (CPC 3 and 4), largely due to the requirement for nursing/residential home care in CPC 3-4 survivors. The estimated annual cost was £3,315 and £43,146 for CPC 1-2 and CPC 3-4 survivors, respectively. See Box 6.2 for a description of the CPC categories, which are frequently used to measure outcomes following OHCA (Elliott, Rodgers and Brett, 2011). It is common practice to combine CPC 1 and CPC 2 into a survival group with good neurological outcome and CPC 3 and CPC 4 into a group with poor neurological outcome (Martinell *et al.*, 2017; Yasunaga *et al.*, 2010). To reflect the significant difference in post-discharge healthcare costs between survivors with CPC1-2 and CPC3-4, the decision tree was further refined to include these different health states; see Figure 6.6.

Box 6.2 Cerebral performance categories used to measure neurologic recovery after out-of-hospital cardiac arrest and other conditions

CPC 1 - Good cerebral performance: conscious, alert, able to work, might have mild neurologic or psychologic deficit.

CPC 2 - Moderate cerebral disability: conscious, sufficient cerebral function for independent activities of daily life. Able to work in sheltered environment.

CPC 3 - Severe cerebral disability: conscious, dependent on others for daily support because of impaired brain function. Ranges from ambulatory state to severe dementia or paralysis.

CPC 4 - Coma or vegetative state: any degree of coma without the presence of all brain death criteria. Unawareness, even if appears awake (vegetative state) without interaction with environment; may have spontaneous eye opening and sleep/awake cycles. Cerebral unresponsiveness.

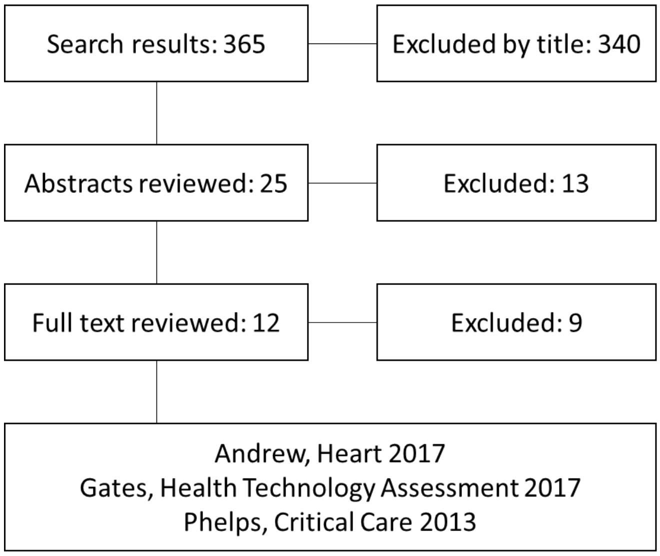
CPC 5 - Brain death: apnea, areflexia, EEG silence, etc.

CPC: Cerebral Performance Category, EEG: Electroencephalogram

6.2.6.7 Post-discharge outcomes

As the data from my observational research were limited to the primary outcome of survival to hospital discharge, both quality and length of life had to be estimated from previously published work. I undertook a focused literature search in PubMed, using the search string *(((quality of life[MeSH Terms]) OR utility) OR life expectancy[MeSH Terms]) AND cardiac arrest[MeSH Terms]*, with search results limited to the last 10 years. Inclusion criteria were adult non-traumatic OHCA and outcomes of either length or quality of life measured in utility. Where available, publications using data from the UK were included; where no UK data were available, data from North America or Australia were deemed sufficient. See Figure 6.4 for a flow chart of the literature review.

Figure 6.4 Focused literature search for data on length and quality of life following out-of-hospital cardiac arrest



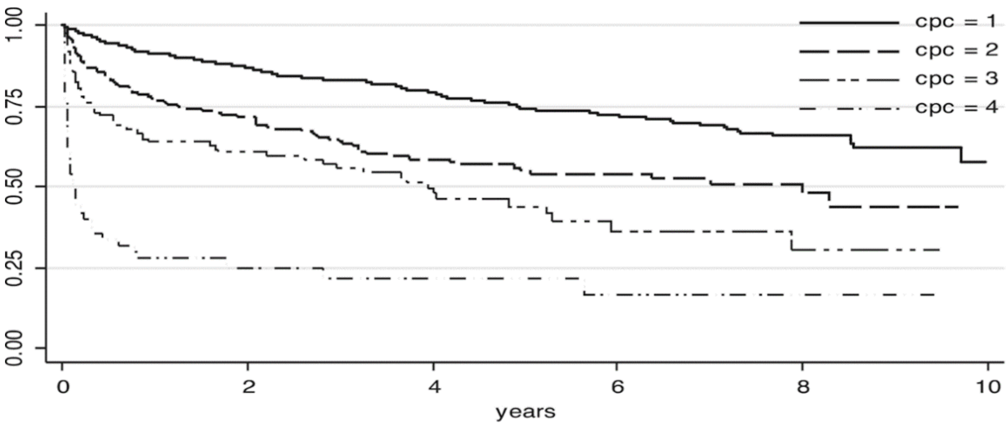
The two questions required for the decision tree and Markov model were:

- What is the proportion of CPC 1-2 and CPC 3-4 amongst OHCA patients discharged from hospital alive?
- What is the quality and length of life of survivors of OHCA with CPC 1-2 and CPC 3-4, respectively?

Proportions of CPC 1-2 and CPC 3-4 amongst survivors to hospital discharge

Gates *et al.* (2017) provide the most current and relevant information in their randomised controlled trial and embedded economic analysis of mechanical CPR during OHCA in the UK. CPC was measured at 3 months after discharge from hospital, with 245 of 272 (90%) of patients achieving a CPC 1-2. This is somewhat higher than the 78% and 85% of CPC 1-2 survivors reported by Petrie *et al.* (2015a) and (Phelps *et al.*, 2013) in a UK and Australian patient population, respectively. However both of these studies measured CPC at hospital discharge, rather than at 3 months after discharge. Figure 6.5 shows that patients discharged from hospital after OHCA with CPC 3-4 have a significantly higher mortality in the first months post-discharge when compared to those discharged with CPC 1-2. Additional data from Phelps *et al.* (2013) at 12 months post-discharge demonstrate that, of the 804 patients who survived to 1 year post-discharge, 90% were discharged from hospital with CPC 1-2. I therefore decided that 85% was a robust estimate for the percentage of OHCA survivors discharged with CPC 1-2.

Figure 6.5 Kaplan Meier survival curve of patients discharged from hospital after out-of-hospital cardiac arrest, according to Cerebral Performance Category (CPC) Phelps *et al.* (2013), with permission from Critical Care (license number 4252320818003)



Length of life of survivors with CPC 1-2 and CPC 3-4

Phelps *et al.* (2013) also provide the most detailed description of long-term survival following OHCA, according to CPC at discharge from hospital, including person-years for the first year and the following 4 years after hospital discharge. See Table 6.3 for a summary of survival rates and person-years.

Table 6.3 Survival rates and person-years according to Phelps *et al.* (2013)

	Year 1		**Year 1-5**	
	Survival (95% CI)	Person-years (per 100 discharges*)	Survival (95% CI)**	Person-years (per 100 discharges per year*)
CPC 1-2	87.4% (85.0% - 89.5%)	78.5	84.6% (81.8% - 87.1%)	241.1
CPC 3-4	51.7% (43.7% - 59.6%)	9.39	79.0% 68.5% - 86.6%)	24.7

**Assuming 85% of survivors to discharge have CPC 1-2 and 15% have CPC 3-4 at hospital discharge.*
*** Percentage of survivors at 5 years per survivors at 1 year.*
CPC: Cerebral Performance Category

The information in Table 6.3 was used to model mortality during the first 5 years after discharge from hospital following OHCA (Phelps *et al.*, 2013). Survival rates after 5 years following discharge from hospital after OHCA have been shown to be the same as those of the standard population (Andrew *et al.*, 2017; Phelps *et al.*, 2013). Mortality rates were therefore obtained from the National Life Tables for England (Office for National Statistics, 2016) and applied to the patient cohort from 5 years onwards. This resulted in an overall survival rate of 65.0% and 50.0% (CPC1-2) and 36.0% and 27.8% (CPC3-4) at 10 and 15 years post-discharge, respectively.

Quality of life

In their RCT which recruited a total of 4,471 patients with OHCA between 2010 and 2013 in four UK ambulance services, Gates *et al.* (2017) reported health-related quality of life (HRQL) using the EuroQol – five-dimension descriptive system (EQ-5D). The EQ-5D has been validated for measuring HRQL and for use in economic evaluations in a variety of conditions, including cardiac arrest (Payakachat, Ali and Tilford, 2015). Gates *et al.* (2017) converted their findings to health-state utilities using the UK tariff. Using a combination of decision tree and Markov model similar to the one used in this research, they calculated a utility of 0.75 and 0.47 for the CPC 1-2 and CPC 3-4 group, respectively. Use of EQ-5D for the calculation of utility is recommended by NICE (National Institute for Health and Care Excellence, 2013).

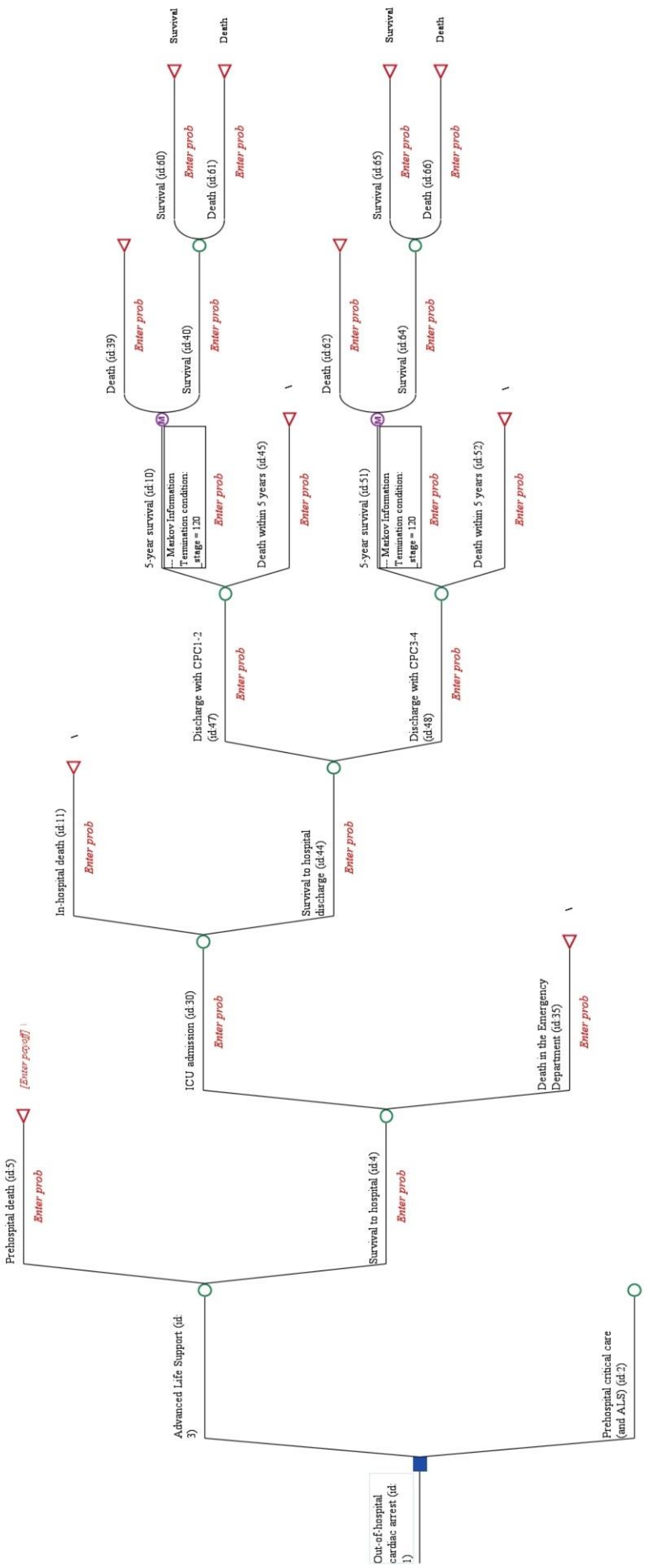
6.2.7 Adjustments of the analytic model

As described in the previous section, a review of the relevant literature identified additional patient pathways following OHCA which needed to be incorporated into the model due to their potentially significant impact on the costs and effects of treatment options. Compared to the initial model in Figure 6.2, the final analysis model in Figure 6.6 includes the following additional pathways:

- Death in the Emergency Department, due to significantly lower costs compared to patients admitted to ICU.
- Discharge from hospital in either good or poor neurological state (CPC1-2 and CPC3-4, respectively), due to considerably higher costs and lower health utility in the CPC3-4 group.
- Modelling of long-term survival using a Markov model, to reflect the accumulation of costs and utility following survival after OHCA. Markov models are commonly used to model long-term outcomes, such as survival, in decision analysis in health economics (Briggs, Claxton and Sculpher, 2006). In short, analysists can set probabilities for patients transferring from one health state to another over a certain period of time (in this case, transition from survival to death was modelled in annual

cycles). The Markov model then runs repeatedly, either until a predetermined end-point is reached, or, in this model, until there are no more survivors. Costs and effects are accumulated and summed up during the process, which includes discounting of future costs and effects.

Figure 6.6 Final analytic model of prehospital critical care following out-of-hospital cardiac arrest, combining decision tree and Markov model; the full pathway is only shown for Advanced Life Support option, due to limited space; the omitted branches following the prehospital critical care option are identical to the ones following the Advanced Life Support option; see Appendix B1



6.2.8 Application of values and distributions to the model

In Section 6.2.6, I described the evidence synthesis process for the data underlying this decision analysis model of prehospital critical care for OHCA. Table 6.4 provides a comprehensive list of all model parameters, based on this process and the assumptions outlined in Section 6.2.6. These parameters (mean values and distributions) were entered into the decision tree and Markov model displayed in Figure 6.6.

Prior to inclusion in the model, all costs were adjusted to Pound Sterling for the financial year 2016-17 according to the UK Hospital and Community Health Services (HCHS) pay and prices index (Department of Health, 2016b). In keeping with NICE guidelines, an annual discount rate of 3.5% was applied to costs and effects which occurred after the first year following discharge from hospital (National Institute for Health and Care Excellence, 2013).

To reflect the uncertainty in available data, confidence intervals or interquartile ranges were transferred to sampling distributions according to the recommendations by Briggs, Claxton and Sculpher (2006). For probabilities and utilities, beta distributions, which are constrained to between zero and one were chosen. Gamma distributions were applied to survival and cost data; they contain continuous variables from zero to infinity. For survival rates following 5 years from discharge, exact values were chosen, as they are based on national statistics with very little uncertainty.

In addition to these distributions used for probabilistic sensitivity analysis, costs of prehospital critical care and the proportion of survivors discharged from hospital after OHCA with either CPC1-2 or CPC3-4 was subject to a two-way sensitivity analysis. This additional manual sensitivity analysis was undertaken to reflect the fact that prehospital critical care is likely to vary in costs in different regions and that the intervention might shift the ratio of CPC1-2 to CPC3-4 survivors when compared to ALS, with important implications on cost-effectiveness. Costs of prehospital critical care were varied up to 20% above and below the estimate; the ratio of CPC1-2 to CPC3-4 survivors was varied from the mean 5.7 (85% CPC1-2) to ratios of 3 (75% CPC1-2), 4 (80% CPC1-2) and 9 (90% CPC1-2).

Table 6.4 Values and distributions of parameters of the decision tree and Markov model; all costs adjusted for inflation to the financial year 2016-17

Parameters	**Cohort/ patient group**	**Mean value (95% CI)**	**Distribution**	**Source**
Prehospital (decision tree model)				
Costs of prehospital care	ALS	£347	Gamma	Trust Alpha PCC-1
	Critical care	£2,058	Sensitivity analysis	
p survival to hospital arrival	ALS	25.8% (24.6% – 27.0%)	Beta	Simulated data
	Critical care	21% – 33%, 2% intervals	Sensitivity analysis	
In-hospital (decision tree model)				
Costs of ED treatment		£377 (£355 – £399)	Gamma	Department of Health (2016a)
p ICU admission*		0.65 (0.58 – 0.71)	Beta	Benger *et al.* (2016)
Costs of ICU treatment (daily) and length of stay (LOS) on ICU	Survival to hospital discharge	£1,745 (£1,654 – £1,836) LOS (days) 5.7 (5.4 – 6.0)	Gamma	Petrie *et al.* (2015b) Nolan *et al.* (2016)
	In-hospital death	£1,768 (£1,668 – £1,868) LOS (days) 2.4 (2.3 – 2.5)		
Cost of non-ICU treatment (total)	Survival to hospital discharge	£12,823 (£10,123 – £15,523)	Gamma	Petrie *et al.* (2015b) Nolan *et al.* (2016)
	In-hospital death	£3,835 (£3,045 – £4,625)		
p survival to hospital discharge	ALS	9.0% (8.2% - 9.7%)	Beta	Simulated data
	Critical care	9% – 15%, 1% intervals	Sensitivity analysis	
Post-discharge (decision tree model)				
p survival with CPC1-2**		0.85 (0.826 – 0.871)	Beta and sensitivity analysis	Phelps *et al.* (2013)
p 5-year survival	CPC1-2	0.740 (0.709 – 0.768)	Beta	Phelps *et al.* (2013)
	CPC3-4	0.408 (0.332 – 0.489)		
Person-years per death within 5 years	CPC1-2	1.827 (1.750 – 1.878)	Gamma	Phelps *et al.* (2013)
	CPC3-4	0.313 (0.254 – 0.375)		
Utility	CPC1-2	0.75 (0.70 – 0.80)	Beta	Gates *et al.* (2017)
	CPC3-4	0.47 (0.42 – 0.52)		
Annual healthcare costs	CPC1-2	£3,358	Gamma	Gates *et al.* (2017)
	CPC3-4	£43,670		
Long-term outcomes (Markov model)				
p annual mortality after 5 years post-discharge	CPC1-2	National age-adjusted mortality rates	Gamma	Office for National Statistics (2017)
	CPC3-4			

**of survivors to hospital **of survivors to hospital discharge*
CI: Confidence interval, ALS: Advanced Life Support, PCC: Prehospital critical care service, ED: Emergency department, p: probability, ICU: Intensive care unit, CPC: Cerebral Performance Category

6.2.9 Probabilistic and parameter-specific sensitivity analysis

The decision analysis model (Figure 6.6) and the underlying uncertainty of the data (Table 6.4) were analysed through the use of Monte Carlo simulations, using TreeAge (version 2017, TreeAge Software). For each parameter in the model, the value used in the analysis is chosen randomly from the assigned distribution of the parameter for a given iteration. The programme records the resulting costs and effects, before beginning the next iteration, in which values are again chosen randomly from each distribution (Briggs, Claxton and Sculpher, 2006). The resulting variations in estimates of costs and effectiveness result in a mean estimate and normal distribution of costs and effectiveness, allowing decision makers to assess the probability of the intervention being cost-effective at any given threshold of willingness to pay.

6.3 Results

6.3.1 Prehospital costs

Table 6.5 gives an overview of the costs of prehospital ALS care and prehospital critical care for OHCA. The average cost of a prehospital critical care team attending a patient with OHCA is £1,711, compared to £347 for ALS prehospital care. As all patients with OHCA who receive prehospital critical care are also receiving ALS prehospital care, the total cost for prehospital critical care per patient with OHCA, used in the following analyses, is £2,058.

Table 6.5 Prehospital treatment costs for out-of-hospital cardiac arrest

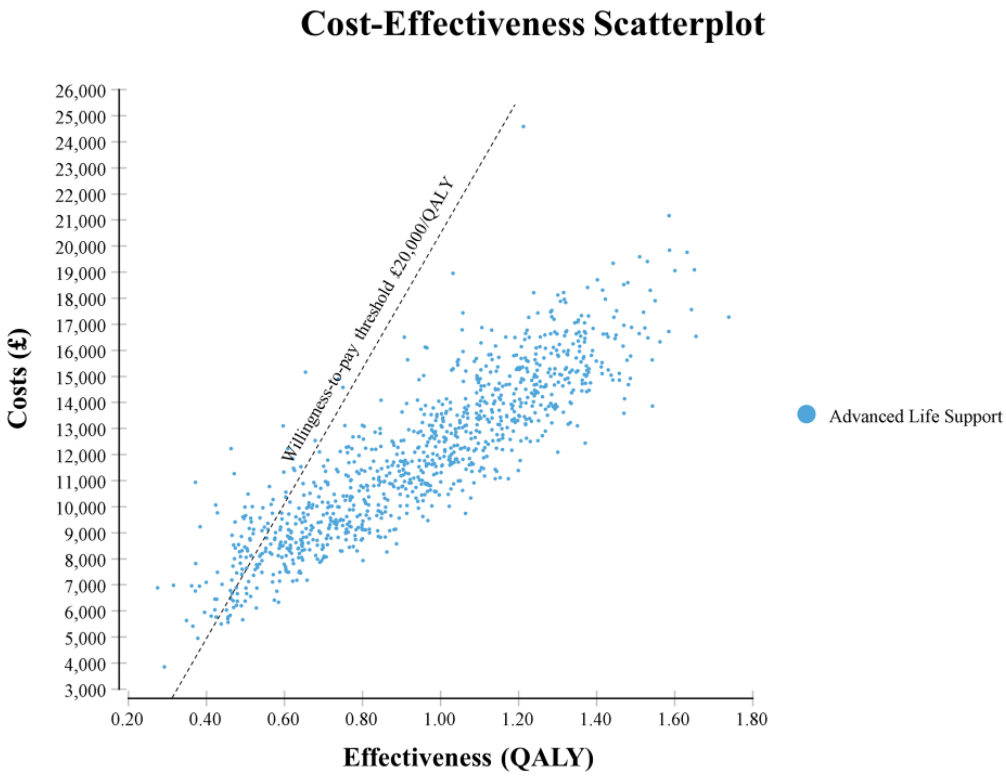
Total expenditure in 2015-16 (in £)		
	ALS care	**Critical care**
Staff costs	36,732,844	665,293
Vehicles (including fuel)	8,145,245	13,659
Helicopter (including fuel)	-	1,318,432
Buildings	2,705,442	37,693
Equipment	1,681,383	63,296
Other	6,261,901	37,752
Dispatch centre	2,226,955	45,000
Total	**57,753,770**	**2,181,125**
Expenditure related to OHCA in 2015-16		
Percentage of resources devoted to OHCA	0.85%	32.9%
Number of OHCA patients in 2016	1412	388
Cost per OHCA patient	**£347**	**£1,711**

ALS: Advanced Life Support, OHCA: Out-of-hospital cardiac arrest

6.3.2 Cost-effectiveness of Advanced Life Support for out-of-hospital cardiac arrest

The cost-effectiveness of the current standard pathway for OHCA, including prehospital ALS, hospital admission, ICU and non-ICU treatment as well as post-discharge healthcare costs is £11,407/QALY (IQR £6,840/QALY – £16,863/QALY). Figure 6.7 shows the corresponding scatterplot with results from 1,000 iterations of the probabilistic sensitivity analysis. Each blue dot represents the result of cost and effectiveness of one iteration. Results to the right of the dotted WTP threshold are considered cost-effective at the chosen WTP threshold of £20,000 per QALY (98.1% of iterations).

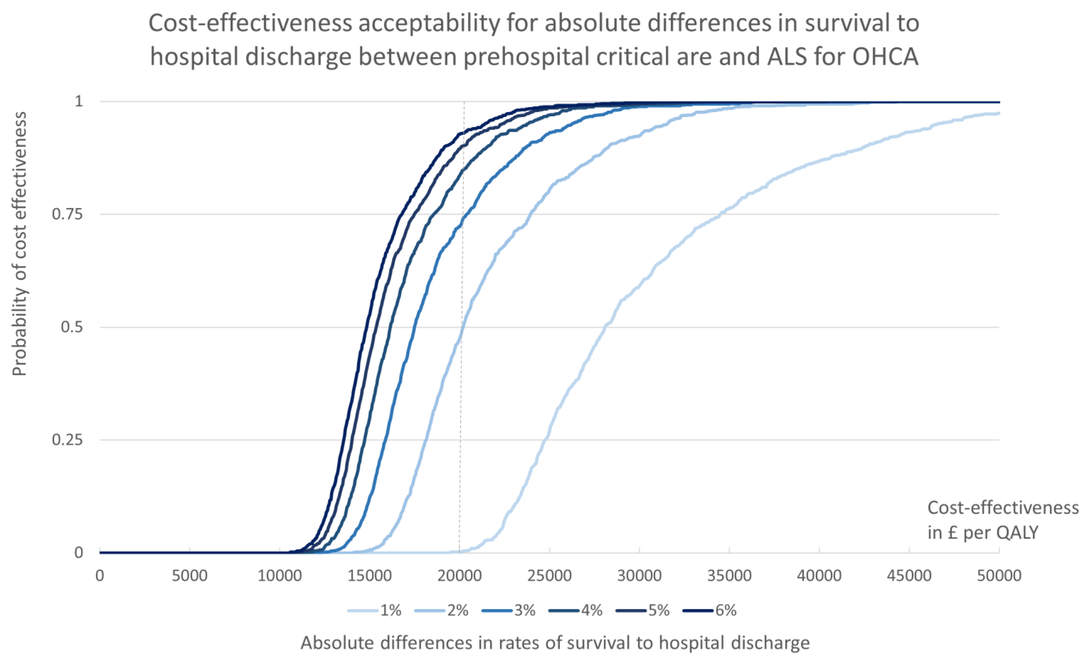
Figure 6.7 Scatterplot of the cost-effectiveness of Advanced Life Support for out-of-hospital cardiac arrest



6.3.3 Incremental cost-effectiveness of prehospital critical care

Figure 6.8 shows the cost-effectiveness acceptability curves for a number of potential treatment effects of prehospital critical care following OHCA. Similar to the data presented in the cost-effectiveness scatterplot in Figure 6.7, cost-effectiveness acceptability curves are the results of 1,000 iterations during the probabilistic sensitivity analysis, using the parameter distributions from Table 6.4. The probability of cost-effectiveness on the y-axis of the graph in Figure 6.8 is calculated from the proportion of iterations which fall below the corresponding WTP threshold on the x-axis. For example, assuming a 2% improvement in survival from OHCA with prehospital critical care and a WTP threshold of £20,000 per QALY, the probability of cost-effectiveness of prehospital critical care is 50%, as 500 iterations were below and 500 iterations were above this WTP threshold.

Figure 6.8 Cost-effectiveness acceptability curves of different treatment effects of prehospital critical care for out-of-hospital cardiac arrest, when compared to Advanced Life Support (baseline survival to hospital discharge for the Advanced Life Support cohort is 9%)



ALS: Advanced Life Support, OHCA: Out-of-hospital cardiac arrest

For the model underlying the cost-effectiveness acceptability curves in Figure 6.8, the ratio of rates of survival to hospital arrival and survival to hospital discharge in the prehospital critical care treatment arm was kept constant. When compared to ALS with a survival to hospital arrival rate of 25% and a rate of survival to hospital discharge of 9%, prehospital critical care needs to achieve a 2% or 3% absolute increase in survival to hospital discharge to have a 48% or 72% probability of being cost-effective at a WTP threshold of £20,000 per QALY, respectively. With a lower absolute difference in survival rates of 1%, prehospital critical care has a less than 1% probability of being cost-effective at the same WTP threshold. Higher absolute differences in survival of 4%, 5% and 6% result in probabilities of cost-effectiveness at the WTP threshold of £20,000 of 84%, 90% and 93%, respectively.

The results of the analysis presented in Figure 6.8 assume that the rates of survival to hospital arrival increase proportionally with the rates of survival to hospital discharge. However, as the majority of costs for the care of OHCA are generated by in-hospital treatments, variations in the rate of survival to hospital arrival can have considerable influence on costs, independent of later survival to hospital discharge. Table 6.6 provides estimates and 95% confidence intervals for possible combinations of survival to hospital arrival and survival to hospital discharge rates.

Table 6.6 Incremental cost-effectiveness of prehospital critical care for out-of-hospital cardiac arrest, for different rates of survival to hospital arrival and survival to hospital discharge, compared to Advanced Life Support

Difference in rates of survival to hospital arrival	**Difference in rates of survival to hospital discharge Median (95% confidence interval)**					
	+1%	**+2%**	**+3%**	**+4%**	**+5%**	**+6%**
-5%	**25,000** (16,500 – 46,000)	**18,000** (12,500 – 28,500)	**15,500** (11,000 – 23,500)	**14,500** (10,500 – 21,000)	*Not achievable*	*Not achievable*
0%	**27,500** (20,000 – 47,500)	**19,000** (14,500 – 30,000)	**16,500** (12,500 – 24,500)	**15,000** (11,500 – 22,000)	**14,000** (11,000 – 20,000)	**13,500** (10,500 – 19,000)
+5%	**30,500** (21,500 – 53,000)	**20,500** (15,500 – 33,500)	**17,000** (13,000 – 26,500)	**15,500** (12,000 – 23,000)	**14,500** (11,500 – 21,500)	**14,000** (11,000 – 20,000)
+10%	**33,500** (22,500 – 61,000)	**22,000** (16,000 – 37,500)	**18,000** (14,000 – 28,500)	**16,500** (12,500 – 24,500)	**15,000** (12,000 – 22,000)	**14,500** (11,500 – 21,000)
+15%	**36,500** (23,000 – 70,500)	**23,500** (17,000 – 42,000)	**20,000** (14,500 – 32,000)	**17,000** (13,000 – 26,500)	**16,000** (12,500 – 23,500)	**15,000** (11,500 – 22,000)
+20%	**39,500** (23,500 – 79,500)	**24,500** (17,000 – 46,000)	**20,000** (15,000 – 34,000)	**17,500** (13,500 – 29,000)	**16,500** (12,500 – 25,500)	**15,500** (12,000 – 23,000)

Light and darker shades of grey indicate most likely combination of differences in rates of survival to hospital arrival and survival to hospital discharge, based on the ratio for survival to hospital arrival to survival to hospital discharge of 0.36 observed in the ALS cohort. All costs are in £ and have been rounded to the nearest £500 value.

6.4 Discussion

This is the first economic analysis, based on a decision analysis model, to address the question of cost-effectiveness of prehospital critical care following OHCA. An important limitation of this chapter is the current lack of data on clinical effectiveness of prehospital critical care for OHCA, which will be addressed in the next chapter. Nevertheless, the economic analysis presented here provides new and important data which can inform some of the discussions between stakeholders, described in Chapter 5.

6.4.1 Costs of prehospital care for out-of-hospital cardiac arrest

Much of the discussion around funding of prehospital critical care services during the qualitative research focused on how much is currently spent and how much prehospital critical care would cost. Given the complexity of the economic analysis of the whole OHCA pathway, it is worth looking first at prehospital resource use only. The ambulance service described in this chapter has an annual spending of over £50 million. However, during the study period, patients with OHCA represented only 0.22% of all emergency calls attended by the section of Trust Alpha. This was a fact repeatedly pointed out by the ambulance service commissioners during the focus group interview. Even when the requirement of additional resources for OHCA patients, compared to most other prehospital conditions, was considered, only an estimated 0.82% of the annual spending was allocated to OHCAs, at an estimated cost of £347 per patient with OHCA. From a patient and public involvement perspective, this would seem to be a rather low amount of money to be spent on the immediate care of a life or death situation.

In contrast, the annual cost of providing a helicopter-based prehospital critical care team, covering the same geographic area, was relatively low, at just over £2 million per year. Due to the fact that the critical care team see far fewer patients (approximately 1,200 during the study period) with a higher proportion (approximately 30%) of OHCAs, the incremental costs of prehospital critical care per OHCA were estimated at £1,711. Given the gravity of the acute situation of an OHCA, the perceived clinical and non-clinical benefits cited by the PPI group, air ambulance charity representatives and prehospital providers, this incremental cost might be considered an effective use of EMS resources. However, focusing only on the prehospital costs of OHCA would make comparison to other healthcare interventions difficult and would ignore the importance of costs accumulated further along the OHCA pathway.

6.4.2 Costs of the out-of-hospital cardiac arrest pathway

While the focus of this research is the costs and effectiveness of prehospital critical care for OHCA, a few important observations on the costs of in-hospital care and post-discharge resource use should be noted.

For patients with OHCA where resuscitation is unsuccessful and who are declared dead on scene no further costs, other than those described in the previous section, occur. On the other hand, a large proportion (25% in the preliminary ALS cohort) of patients with OHCA survive the prehospital phase of their care and are admitted to a hospital. If active treatment is continued in hospital, patients are admitted to ICU, where the costs of a single day's care is about the same as that of a prehospital critical care team attending the patient. On average, I estimated the costs of in-hospital treatment to be approximately £22,000 for patients surviving to hospital discharge and £8,500 for patients who die in hospital. The major contributors to these costs are ICU-bed days (all patients) and interventions such as PPCI, ICD implantation or coronary artery bypass graft surgery (survivors only).

Further costs can accumulate after hospital discharge; most importantly the long-term care services required for the small proportion of patients who survive to hospital discharge with poor neurological function (over £40,000 per year). The magnitude of downstream costs in the OHCA pathway, compared to the prehospital costs alone, emphasise the importance of analysing the complete pathway, which I was able to do through the use of decision analysis modelling as described in Section 6.2. The following paragraphs will now focus on the results of this complete pathway analysis.

6.4.3 Cost-effectiveness of Advanced Life Support for out-of-hospital cardiac arrest

Utilising data from publications most relevant to the UK population and current EMS systems' configuration, I was able to estimate the cost-effectiveness of paramedic-delivered ALS for OHCA to be approximately £11,500 per QALY. With the upper limit of the interquartile range at approximately £16,800, this makes ALS for OHCA almost certainly cost-effective at a NICE WTP threshold of £20,000 per QALY (National Institute for Health and Care Excellence, 2013).

While a number of previous publications address the cost-effectiveness of individual aspects of prehospital care or hospital care for OHCA (Marti *et al.*, 2017; Moran *et al.*, 2015; Merchant *et al.*, 2009), very few address the cost-effectiveness of ALS for OHCA in the context of the complete patient pathway. Naess and Steen (2004) estimated that the cost-effectiveness of ALS for OHCA in Norway was €6,632 (approximately £6,000) per QALY. This much lower estimate is likely due to inflation (since the year of publication was 2004) and recent developments in hospital-based post-cardiac arrest care, with higher rates of intervention and associated higher costs (Nolan *et al.*, 2016; Lai *et al.*, 2015).

More recently, Ginsberg, Kark and Einav (2015) reported the cost-effectiveness of ALS for OHCA to be $28,864 per Disability Adjusted Life Year (DALY) averted, in an Israeli EMS system. The conversion from DALY averted to QALY gained depends on many factors and, in this context, probably ranges between 0.7 to 1.3 (Sassi, 2006). The corresponding value for the cost-effectiveness calculated by Ginsberg, Kark and Einav (2015) is therefore likely to be in the range of £15,000 - £28,500 per QALY. As neither of these studies were undertaken in the UK setting, transferability of the results is difficult.

Within the limitations of the research presented here, as well as taking previous research findings into account, it is fairly certain that paramedic-delivered ALS is a cost-effective treatment for OHCA in the UK. Furthermore, in terms of £ per QALY, it compares favourably with a range of interventions currently funded by the NHS (Pharoah *et al.*, 2013; Hartwell *et al.*, 2005).

6.4.4 Investigating cost-effectiveness of prehospital critical care

The purpose of creating this decision analysis model is to assess the cost-effectiveness of prehospital critical care for OHCA. Once the effectiveness data are available in the next chapter, I will input this data to the model and present the results at that stage. In the meantime, running the model with probabilistic sensitivity analysis and various assumptions allowed me to examine the impact of prehospital critical care on downstream costs and to predict a minimally economically important difference in survival rates, which I can use to test the appropriateness of my sample size in the next chapter.

Using the cost-effectiveness acceptability framework in Figure 6.8 (Gray *et al.*, 2011) , I have shown that the minimally economically important difference in survival rates after OHCA depends on the stakeholders' willingness-to-pay threshold as well as the degree of certainty they consider suitable to make a funding decision. For example, if one wanted to be 90% certain that prehospital critical care is a cost-effective intervention for OHCA, at a willingness-to-pay threshold of £20,000 per QALY, research would need to be powered to detect an absolute improvement in survival rates from approximately 9% to 14%, when compared to ALS care. On the other hand, a 1% absolute difference in survival with prehospital critical care, which could only be ruled out with a very large sample size, has a less than 1% chance of being cost-effective.

In addition to rates of survival to hospital discharge, the cost of prehospital critical care is considerably influenced by the associated rates of survival to hospital arrival, as shown in Table 6.6. For example, an improvement in survival to hospital discharge of 2% might be cost-effective, if the prehospital critical care team achieves this effect without increasing the proportion of patients admitted to hospital. This could be achieved through clinical decisions to switch to palliative treatment in patients with ROSC but also factors such as a poor quality of life or significant co-morbidities which suggest that further treatment is not in the patient's best interest. However, if the increase in survival to hospital discharge of 2% is due to a higher rate of ROSC and survival to hospital arrival, as a result of the interventions provided by the prehospital critical care team, the cost-effectiveness is decreased (due to the associated hospital treatment costs), and prehospital critical care is now unlikely to be cost-effective.

NICE does not stipulate a fixed threshold for cost-effectiveness, but states that factors other than costs are considered in the decision-making process for funding recommendations (National Institute for Health and Care Excellence, 2013). However, a common interpretation of the NICE guidance is that interventions costing less than £20,000 per QALY should be adopted as cost-effective (Appleby, 2016). For interventions with an incremental cost-effectiveness ratio (ICER) of £20,000 to £30,000 per QALY additional considerations, such as the strength of the evidence, should be considered but cost-effectiveness is unlikely (Appleby, 2016; Claxton *et al.*, 2015). Interventions with an ICER higher than £30,000 per QALY are generally not recommended for implementation in the NHS, with the notable exception of interventions delivered in end-of-life situations and the Cancer Drugs Fund (Leigh and Granby, 2016; Cookson, 2013).

Combining the above variables and information, Table 6.6 would suggest a minimally economically important difference in survival rates after OHCA of 4%, when comparing prehospital critical care to ALS. The research underpinning the clinical effectiveness of prehospital critical care will be of observational design. Therefore, funders would want to be certain that the estimated ICER is well below the threshold of £30,000 per QALY. As can be seen in Table 6.6, an absolute improvement in survival of 4% with prehospital care is the minimal clinical effect at which the 95% confidence intervals for the ICER estimation do not include £30,000 per QALY and the point estimates are below £20,000 per QALY. 4% is therefore the treatment effect of prehospital critical care which the observational research presented in the next chapter should be powered to detect.

6.5 Challenges and limitations

The most important limitation of this economic analysis is the fact that it is largely based on a theoretical construct of the costs and effects of the care pathway for OHCA. As such, certain assumptions about what happens in reality had to be made and must be assumed to reflect reality accurately, in order for the model to be internally valid (Briggs, Claxton and Sculpher, 2006). Nevertheless, any model will always be a simplification of reality.

6.5.1 Accuracy of the costing data

I did not adapt a micro-costing approach which would have, for example, included recording the exact number of paramedics at scene for an OHCA, the amount of drugs or therapeutics used and so on. Such an approach would have likely resulted in a more accurate estimate of the costs of ALS care for OHCA overall, but would have required tremendous efforts to collect and analyse the data. Gray *et al.* (2011) suggest that the consideration of micro- versus gross-costing should be guided by the research team's prior knowledge of the interventions and costs studied. It became clear early on that the main drivers of costs were those of hospital and post-discharge treatments. Within the prehospital phase, staff and vehicle costs dominated resource use for OHCA (see Table 6.5). At the same time, clinical experience suggested that the prehospital resource use for OHCA varied considerably between individual cases. Using a micro-costing approach would therefore be unlikely to change the cost estimate for prehospital care significantly and, unless undertaken in a large sample, might actually be less accurate than the average annual data used in the methods in this chapter. Reassuringly, the estimated cost of £347 for ALS care for OHCA compares realistically to the NHS National Schedule of Reference Costs of an average of £236 for *"see and treat and convey"* ambulance activities (Department of Health, 2016a).

The same consideration of micro- versus gross-costing applies to the estimate of costs of prehospital critical care for OHCA. The main driver of the costs in this treatment arm of the model was the helicopter, followed by staff. A previous economic analysis of five different HEMS systems in the UK indicated annual costs of £55,000 to £1,200,000 in 1996, which, after adjusting for inflation, corresponds to approximately £100,000 to £2,200,000 in 2016 (Department of Health, 2016b; Snooks *et al.*, 1996). The higher end of the cost range in the study by Snooks *et al.* (1996) referred to the London Air Ambulance, which would have been the only air ambulance in 1996 providing a service comparable to modern air ambulance practice (Kirk *et al.*, 1993).

6.5.2 Accuracy of the decision analysis model

In regards to the validity of the overall model, there is little previous literature to compare to. Delgado *et al.* (2013) used a similar decision model analysis approach to examine the potential cost-effectiveness of a HEMS system for trauma cases in the US. They found that a 1.6% and 3.7% absolute decrease in mortality was required for the HEMS system to be cost-effective at WTP thresholds of $100,000 and $50,000, respectively. While Delgado *et al.*

(2013) examined a different condition in a different healthcare setting, the similarity of results is reassuring.

When critically reviewing the decision analysis model presented in this chapter, I identified two assumptions with a potentially significant impact on the cost-effectiveness results.

The first is the configuration of the prehospital critical care team, utilising a helicopter. There was a strong perception by ambulance service commissioners and, to a lesser degree, prehospital researchers (Chapter 5), that a helicopter was a very expensive commodity in prehospital care. This is certainly true for this model, where over 50% of the prehospital critical care costs stemmed from the use of a helicopter. However, a number of prehospital critical care services use only rapid response vehicles (RRVs), with considerably less costs compared to a helicopter (Younger, 2015). So is the cost estimate of prehospital critical care in this model unrealistically high? I discussed this issue with my prehospital critical care colleagues. To provide a similar level of coverage (i.e. reaching the same amount of patients within a similar timeframe) of the section of Trust Alpha area, without a helicopter, they estimated that two to three prehospital critical care teams would need to be stationed in RRVs in different areas. While this configuration would eliminate the costs of a helicopter, it would double or treble the staffing costs, with overall costs potentially similar to the helicopter model. To further address the potential impact of more or less expensive configurations of prehospital critical care, I will undertake a sensitivity analysis in the final model presented in the next chapter, varying costs of prehospital critical care from +50% to -50% (relative differences to the baseline costs).

The other assumption underlying the decision analysis model presented in this chapter is that the ratio of survivors with good (CPC1-2) and poor (CPC3-4) neurological function remains the same in the ALS and prehospital critical care arm. It is possible that prehospital critical care interventions do not change overall survival rates, but lead to an increased proportion of good neurological outcomes amongst the survivors (Yasunaga *et al.*, 2010). Conversely, it might be that prehospital critical care can increase survival rates, but that this increased survival is achieved in patients who then do not achieve good neurological function after discharge (Yasunaga *et al.*, 2010). Given the considerable costs associated with survival with poor neurological function, either scenario might potentially have a significant effect on the cost-effectiveness of prehospital critical care. Unfortunately, neurological function after discharge is not an outcome recorded in the OHCAO Registry used for this research. To address the potential effect of varying proportions of good neurological outcomes in survivors, I will undertake a further sensitivity analysis in the final model presented in the next chapter. I will vary the proportion of good neurological outcomes from +5% to -5% (absolute difference to the baseline rate).

6.6 Conclusions

The current prehospital standard of care for OHCA in the UK; ALS, is cost-efficient, even if the significant downstream costs are included. Adding prehospital critical care to ALS care incurs additional costs which are largely attributable to the costs of a helicopter and staffing of the prehospital critical care team. Incremental cost-effectiveness of prehospital critical care for OHCA depends on a number of factors. Much of the additional cost is determined by resource use further along the OHCA care pathway, in hospital and after hospital discharge. Using cost-effectiveness-acceptability curves and probabilistic sensitivity analysis, I determined that an absolute difference in survival to hospital discharge of 4% is likely to be the minimally economically important difference in outcome. Any smaller effect of prehospital critical care on survival following OHCA is very unlikely to be cost-effective.

6.7 What next?

So far, much of the focus of this thesis has been on providing a detailed context of prehospital critical care for OHCA. The Introduction chapter described the pathophysiology, treatments, outcome and research challenges of OHCA. In the systematic review presented in Chapter 4, I examined the current published literature on the subject of prehospital critical care, including important methodological issues leading to systematic bias. Chapter 5 explored variations in stakeholders' perceptions of research and funding of prehospital critical care. In this chapter, I used decision model analysis to provide further context about costs and effectiveness of ALS and prehospital critical care for OHCA. This information can inform some aspects of the stakeholder discussions and also the analysis of the effectiveness of prehospital critical care which I will focus on in the next chapter.

To complete the work presented in this chapter, a few steps are currently outstanding. First, the information about costs of care for OHCA and the minimally important economically difference in outcomes required for prehospital critical care to be cost-effective can help to fill some of the void of information which facilitated the contrasting views expressed by some of the stakeholder groups in Chapter 5. While it is unlikely to dramatically shift those views which are held with strong conviction, having some actual data to discuss and to challenge current beliefs might be useful in moving towards a common ground. I will therefore distribute a corresponding summary of the results to the participants of the qualitative research phase. Next, in Chapter 7, I will consider whether my sample size is adequate to detect the minimum economically important difference defined in this chapter. Finally, the key information required to determine the cost-effectiveness of prehospital critical care for OHCA will become available in the next chapter. At the end of Chapter 7, I will therefore revisit the decision analysis model and perform the final cost-effectiveness analysis of prehospital critical care for OHCA, including a number of pre-defined sensitivity analyses. Having set the stage with a detailed description, exploration and analysis of context from different perspectives, it is now time to address the key question of this thesis: does prehospital critical care improve survival following OHCA?

7. Original research: the effect of prehospital critical care on survival following out-of-hospital cardiac arrest

7.1 Introduction

Survival after out-of-hospital cardiac arrest (OHCA) is an excellent example of both the triumphs and limitations of modern medicine. On the one hand, death from OHCA due to ventricular fibrillation (VF) can now be avoided in 30-50% of patients, due to community education and training, cardiopulmonary resuscitation (CPR), defibrillation and the arrival of Emergency Services (EMS) providers within minutes (Hawkes *et al.*, 2017; Lindner *et al.*, 2011). Once a heartbeat has been restored, many patients receive intensive care organ support, percutaneous coronary intervention (PCI) and rehabilitation, resulting in a good quality and length of life for many survivors (Elliott, Rodgers and Brett, 2011). On the other hand, for victims of OHCA where the first recorded cardiac rhythm is asystole, the mortality rate remains disappointingly high 97-99% (Andrew *et al.*, 2014). Chapter 1 gives an overview of the different pathophysiological processes responsible for this stark contrast.

There are a multitude of ongoing efforts to improve the care for patients with OHCA, among them the provision of prehospital critical care. Prehospital critical care can be described as a bundle of interventions, based on common sense and extrapolation rather than high quality evidence, delivered by highly trained and experienced prehospital providers; see Chapter 1.

In Chapter 4, I reviewed the current literature regarding the effect of prehospital critical care on survival following OHCA. Of six observational studies identified, three showed benefit from prehospital critical care, when compared to the current standard of treatment in the United Kingdom (UK) - Advanced Life Support (ALS). However, this benefit was moderate at best, studied within different patient groups and, most importantly, there was a high likelihood of bias and confounding favouring prehospital critical care. The three other publications showed no difference in survival between prehospital critical care and ALS but were limited by their insufficient sample sizes. In addition, the applicability of studies from Japan or Scandinavian countries to the UK setting is questionable, due to important differences in EMS systems' configuration, population, geography and the wider healthcare systems that exist within these countries (Lockey, 2009; Langhelle *et al.*, 2004).

Following on from the systematic review, I undertook a qualitative analysis of stakeholders' views of prehospital critical care for OHCA with particular focus on research and funding in this area; see Chapter 5. This research revealed stark differences in the expectations of the effect of prehospital critical care on survival following OHCA. The patient and public representatives and air ambulance charities considered prehospital critical care to be highly beneficial. In contrast, commissioners and academics expressed views of marginal if any gains of prehospital critical care compared to ALS care. As a result of these different perspectives, the stakeholders' attitudes towards researching and funding prehospital critical care for OHCA varied widely. Replacing or at least supplementing stakeholders' current expectations of the effects of prehospital critical care is therefore an important step towards consensus on future funding and research in this area.

In Chapter 6, I presented the results of an economic analysis of prehospital critical care for OHCA, when compared to ALS care. Prehospital critical care is associated with additional costs along the OHCA care pathway. These need to be offset by at least a 4% increase in survival if prehospital critical care is to have an acceptable possibility of being cost-effective.

Supported and framed by the context which I presented in the previous chapters, I will now attempt to answer the question of whether prehospital critical care improves survival following OHCA, when compared to ALS care. Due to the inherent challenges of bias and confounding in observational research design, much of this chapter will be dedicated to the methods chosen to address these challenges. To reduce the complexity of analysis, this chapter will only focus on the overall effect of prehospital critical care on survival following OHCA. Other important questions, such as what prehospital critical care for OHCA actually is, or how any effect on survival might be caused, will be addressed in the following chapter.

7.2 Methods

7.2.1 Developing the protocol

Having established early in the preparation phase for this thesis that a randomised-controlled trial (RCT) of prehospital critical care for OHCA was not feasible, a prospective observational research design was decided upon. From my pilot study, I knew that ambulance trusts collect most of the relevant Utstein variables (see Chapter 1) on OHCAs occurring in their regions (von Vopelius-Feldt, Coulter and Benger, 2015). To avoid duplication of effort and ensure efficient use of resources, the data collection plan used these routine data as much as possible. Initially, the protocol described that transfer of this routine OHCA data would occur from each ambulance trust directly to myself. However, in April 2016 I visited the Clinical

Trials Unit at the University of Warwick to discuss a potential collaboration with the Out-of-Hospital Cardiac Arrest Outcomes (OHCAO) Registry. The OHCAO Registry has been funded by the British Heart Foundation and Resuscitation Council (UK) with the aim of collecting data on all OHCAs in the UK (Perkins and Brace-McDonnell, 2015). The database receives the same Utstein variables from ambulance trusts that I required for this research. In addition, staff at OHCAO undertake data cleaning and cross-checking, combined with data queries to ambulance trusts if required. Collaboration with OHCAO therefore provided significant benefits in regards to data quality, avoided duplicated efforts, and I did not have to personally negotiate data transfers and queries with up to four different ambulance trusts. I had some hesitation, as this research project would be the first external project to utilise OHCAO data, making the success of the project dependant on an untested data sharing pathway. However, after careful deliberation and discussion with the supervision team and steering group, I decided that the benefits of collaboration with the OHCAO Registry outweighed the risks and adjusted the protocol to include data sharing with the OHCAO Registry. Appendix C1 contains the approval letter from the OHCAO steering committee, regarding a data sharing agreement.

In general, the protocol for this prospective observational study had to incorporate a certain amount of flexibility, as many details would only become clear in the process of data collection and analysis. The precise method of data collection for critical care cases, timing of data transfers, handling of missing data and exact data analysis strategies all had to be addressed in a pragmatic fashion and were only finalised over the course of the research.

7.2.2 Participating ambulance trusts

Due to the sensitivity of these data, particularly for charity-funded prehospital critical care providers (see Chapter 5), all participating organisation are anonymised in this thesis. Four potential participating ambulance trusts had been identified in the preparation phase of this thesis and contact had been established with the help of the Research and Development Department of one of the participating ambulance trusts. Due to a variety of reasons, such as the pressures of dealing with steadily increasing 999 call volumes or switching from paper to electronic patient records, ambulance trusts joined the project at different times. In the end, all four of the potential ambulance trusts participated; see Figure 7.1. Details about the model of prehospital critical care delivery in each ambulance trust can be found in Chapter 8.

Figure 7.1 Participating ambulance trusts (anonymised) and corresponding data collection periods

Map of UK ambulance trusts

List of participating ambulance trusts (anonymised) and corresponding data collection periods

Trust Alpha

- September 2016 to October 2017

Trust Beta

- September 2016 to October 2017

Trust Charlie

- December 2016 to May 2017

Trust Delta

- December 2016 to October 2017

UK: United Kingdom

7.2.3 Inclusion and exclusion criteria

Patients aged 18 years or older who suffered a non-traumatic OHCA were included. OHCA was defined as any case where bystander or EMS provider attempted CPR, but does not include cases where patients showed obvious signs of death and therefore no resuscitation was undertaken. Exclusion criteria were cases of OHCA due to trauma, drowning, electrocution or traumatic asphyxia, as well as OHCAs occurring in children. In all of these cases, the pathophysiology leading to OHCA is distinctively different from the significantly more common medical OHCA in adults; see Chapter 1. Similarly, treatment options differ in these OHCAs, as well as the existing evidence or argument for a benefit of prehospital critical care (Evans *et al.*, 2018; El-Assaad, Al-Kindi and Aziz, 2017).

7.2.4 Selection of patients to prehospital critical care or Advanced Life Support

Ideally, the effect of the intervention of prehospital critical care on survival following OHCA would be assessed by allocating patients at random to receive either prehospital critical care or the comparison treatment, ALS. As this was deemed unfeasible, the observational research design takes advantage of a natural experiment, resulting in one group of patients receiving prehospital critical care (in addition to ALS) and the other group receiving ALS only.

In all participating ambulance trusts, emergency calls are received in one or more regional call centres. If an OHCA is either confirmed or highly likely, a response consisting of first responders and ALS trained paramedics is mobilised as quickly as possible. Patients with OHCA receiving this level of care were assigned to the ALS care group in this research.

In all ambulance trusts, a dedicated dispatcher monitors incoming calls and assesses the likelihood of prehospital critical care being required and beneficial to the patient. The decision to dispatch a prehospital critical care resource is based on either standard criteria or an assessment of the information available at the time of the 999 call, or a combination of the two. In the case of OHCA, factors potentially influencing this decision are the age of the patient, location of OHCA, witnessed status or the presence of bystander CPR. If the decision is made that prehospital critical care is indicated, and a prehospital critical care resource is available, critical care providers are dispatched to the OHCA. Patients with OHCA receiving this level of care were assigned to the prehospital critical care group in this research.

I have demonstrated in Chapter 4 and in my pilot study that this process of dispatch leads to significantly better prognostic factors in the prehospital critical care group (von Vopelius-Feldt, Coulter and Benger, 2015). Therefore, statistical adjustment of relevant Utstein criteria with prognostic value (see Chapter 1) is required for an unbiased estimate of the treatment effect of prehospital critical care for OHCA.

7.2.5 Data collection

Data collection and transfer was split into two data streams. The main source of data was the OHCAO Registry, which received data from each participant ambulance trust's research and audit team. This includes OHCA case identifiers, demographic and outcome data; see Table 7.1. In addition, patient and system factors which might potentially determine whether a patient with OHCA receives prehospital critical care and/or influence survival following OHCA were provided by the OHCAO Registry (Perkins and Brace-McDonnell, 2015; von Vopelius-Feldt, Coulter and Benger, 2015). Table 7.2 provides an overview of these Utstein variables, and their postulated influence on critical care attendance and known effects on survival following OHCA.

Table 7.1 Variables collected via the Out-of-Hospital Cardiac Arrest Outcomes (OHCAO) Registry data stream (Perkins and Brace-McDonnell, 2015)

Variable	**Description**
Ambulance service incident case number	To match case with critical care data stream
Date of emergency medical services call	To match case with critical care data stream
Initial aetiology of cardiac arrest	Inclusion/exclusion criteria
Do Not Attempt Resuscitation order in place	Exclusion criteria
EMS provider chest compressions	Inclusion criteria
Patient's age	Inclusion/exclusion criteria
Patient's gender	Demographic description
Survival to hospital arrival (ROSC sustained to hospital arrival)	Secondary outcome
Survival to hospital discharge	Primary Outcome

EMS: Emergency Medical services, ROSC: Return of spontaneous circulation

Table 7.2 Utstein variables potentially predicting prehospital critical care attendance at out-of-hospital cardiac arrest and/or survival following out-of-hospital cardiac arrest (Perkins *et al.*, 2015a; von Vopelius-Feldt, Coulter and Benger, 2015)

Variable	**Categories**	**Prehospital critical care**	**Survival**
Utstein location of OHCA	Public place Private residence Nursing home	↑ ↔ ↓	↑ ↓ ↓↓
Patient's age	Years of age	↓ with increasing age	↓ with increasing age
OHCA witnessed by?	Unwitnessed Bystander EMS provider	↓ ↑ ↔	↓ ↑ ↑↑
Bystander CPR	Yes/No	↑ if yes	↑↑ if yes
AED used by bystander	Yes/No	↔	↑↑ if yes
1st EMS resource response time	Continuous in minutes and seconds	↔	↓↓ with increasing times
Initially recorded cardiac rhythm	VF or VT (shockable) PEA asystole	↑ ↔ ↓	↑↑ ↔ ↓↓
Time of 999 call	7am – 7pm 7pm – 1am 1am – 7pm	↑ ↓ ↓↓	↔ ↔ (↓)

OHCA: Out-of-hospital cardiac arrest, EMS: Emergency Medical Services, CPR: Cardiopulmonary resuscitation, AED: Automated external defibrillator, VF: Ventricular fibrillation, VT: Ventricular tachycardia, PEA: pulseless electrical activity

In a second data stream, I collected data from all participating prehospital critical care services directly. With the exception of one service, these data were extracted locally from the prehospital critical care service's electronic record keeping system. The remaining service used a paper-based data collection form created for participation in this research. Table 7.3 provides a summary of variables received through this second data stream.

Table 7.3 Data collected directly from prehospital critical care services

Variable	Description
Ambulance service incident case number	To match case with OHCAO data stream
Date of emergency medical services call	To match case with OHAO data stream
Primary tasking or ALS crew request	For intention-to-treat analysis (see Section 7.2.11)
Stand-down en-route	For sensitivity analysis (see Section 7.2.11)
Prehospital critical care doctor present	Background information for Chapter 8
Time of arrival of prehospital critical care team	Background information for Chapter 8
ROSC prior to prehospital critical care team arrival	Background information for Chapter 8
List of prehospital critical care interventions (procedures, drugs, transport decisions, others)	See Chapter 8 for detailed list

OHCAO: Out-of-Hospital Cardiac Arrest Outcomes Registry, ALS: Advanced Life Support, ROSC: Return of spontaneous circulation

7.2.6 Outcomes

The primary outcome was survival to hospital discharge, as recorded in the OHCAO Registry. As discussed in Chapter 1, survival to hospital discharge is a reasonable compromise between a patient-focused outcome and the availability of outcome data. It can, however, be influenced by differences in in-hospital treatments, in addition to the difference in prehospital treatment of critical care or ALS care. Survival to hospital arrival (ROSC on hospital arrival) was therefore chosen as a secondary outcome. It is less patient-focused, but more directly influenced by prehospital interventions.

7.2.7 Propensity score matching

Assignment to the treatment (prehospital critical care) and comparison (ALS care) group in this research is non-random and therefore the treatment effect of prehospital critical care cannot be estimated directly (Guo and Fraser, 2010). In fact, I demonstrated in both the systematic review (Chapter 4) as well as in the pilot study to this thesis that the two groups often show significant differences in important prognostic factors (von Vopelius-Feldt, Coulter and Benger, 2015). To adjust for these differences and reduce the effect of selection bias, I identified propensity score matching as the appropriate statistical method. Propensity score matching can be seen as a stepwise analysis process and I will describe each of the four steps used in the following paragraphs. Prior to this, I will describe the theory and assumptions underpinning propensity score analysis.

7.2.7.1 Causal inference in observational research

The question which this chapter attempts to answer can be slightly rephrased to: does prehospital critical care have a causal effect on survival following OHCA? The challenge is the fact that we can only observe the effects of either prehospital critical care or ALS care on each study subject, never both (Neyman, 1923). As such, we can never know what would have happened to a patient in the prehospital critical care group had they received ALS, or vice versa. The causality of the treatment effect of prehospital critical care when compared to ALS care therefore can never be measured directly, but requires estimation through a counterfactual framework (Neyman, 1923).

The counterfactual framework proposes that the treatment effects equal the difference in outcomes between the treatment and the comparator group, if the allocation to either treatment or comparator is independent of the outcome in either group. This condition is referred to as the strongly ignorable treatment assignment and is assumed to be achieved through randomisation procedures.

In observational research, the assumption of strongly ignorable treatment assignment is frequently violated (Rubin, 2005). Participants or patients are allocated to treatments based on non-random factors, which are frequently associated with the outcome of interest, as demonstrated for prehospital critical care and OHCA in the systematic review presented in Chapter 4. The measured difference in outcomes between treatment and comparator group is therefore confounded and can no longer be used to infer causality (Rubin, 2005). So how can causality be inferred in observational research? The three part definition of causality by Lazarsfeld (1959) is a useful and widely accepted starting point. It states that A can be said to cause B if:

i) A occurs before B (temporal order).

ii) A is empirically correlated with B (association).

iii) The observed correlation between A and B cannot be explained as the results of a third variable C that causes both A and B (lack of bias and confounding).

While condition i) and ii) can easily be examined in observational research, it is condition iii) which makes randomisation the current gold standard for causal inference. However, the definition also shows how causal inference can be achieved in observational research:

measuring all potential confounding variable(s) C1, C2, C3, … and adjusting for their influence on the intervention and/or the outcome of interest (Sterne *et al.*, 2016; Rubin, 2005).

7.2.7.2 Confounding variables and methods of adjustments

The measurement of confounding variables in clinical observational research is largely a matter of knowledge of all relevant variables through theory or review of previous research, as well as having the tools required for measurement (Guo and Fraser, 2010). The effect of these variables can then be referred to as overt (known) bias.

However, in reality it is often difficult to know about and/or measure all important variables, so concerns about hidden (unknown or unmeasured) bias remain an important issue in observational research. The importance of considering all relevant confounding variables was one of the driving factors behind the creation of the Utstein criteria described in Chapter 1. The Utstein criteria include and define the vast majority of variables known to influence survival after OHCA (Perkins *et al.*, 2015a). Once confounding variables have been measured with sufficient accuracy, the association between intervention and outcome in observational research can be adjusted accordingly. Common methods used for such adjustment in clinical research include matching, multiple logistic regression and, more recently, propensity score analysis (Guo and Fraser, 2010). Table 7.4 gives an overview of the strengths and limitations of each method. It is worth noting that none of these methods can fully control for unmeasured or hidden bias (Holmes, 2014).

Table 7.4 An overview of matching, multiple logistic regression and propensity score analysis

Method of adjustment	Advantage	Disadvantage
Matching	• Achieves excellent balance of covariates • Counterfactual framework is applicable	• Difficult or potentially impossible with large number of covariates • Loss of power due to unmatched cases or unused controls
Regression analysis	• Can handle large number of covariates • Easy to undertake in most statistical packages	• Does not adjust for unmeasured confounders (hidden bias) • Temptation for researcher to adjust model towards desired outcome • Unreliable if number of events (positive or negative outcomes) is small
Propensity score analysis	• Can handle large number of covariates • Counterfactual framework is applicable • Outcome analysis independent from model fitting • Can partially adjust for hidden bias	• Requires multiple steps of analysis and more advanced statistical packages • Balancing of covariates not always achieved • Loss of power due to unmatched cases or unused controls

7.2.7.3 Theory of propensity score matching

As outlined in Table 7.4, propensity score matching has a number of advantages over the other two commonly used methods of adjustment in quasi-experimental research; matching and regression analysis (Guo and Fraser, 2010).

The concept of directly matching treatment cases to untreated cases on covariates which independently predict the outcome has been used extensively in medical research (Anglemyer, Horvath and Bero, 2014). Direct matching results in excellent balancing of covariates between the two groups (treated and untreated) (Burden *et al.*, 2017). Going back to the definition of causality by Lazarsfeld (1959), this means that the difference in outcome between the groups will not have been caused by the specified covariates. Provided all relevant covariates have been well measured, causality can therefore be assumed for the effect of treatment on outcome (Rubin, 2005). The main limitation of matching is that it can become next to impossible to find matches between treated and untreated cases as the number of covariates increase even slightly (Guo and Fraser, 2010). Matched groups would potentially only include a fraction of the original sample, resulting in reduced power and a large amount of data not being used for analysis (Faresjö and Faresjö, 2010). Such a fraction of data may also be unrepresentative of the target population, leaving further possibilities of bias.

These problems can be avoided by using regression analysis, which can include a large number of variables and uses all cases in a given dataset for analysis. As the number of Utstein variables used to predict survival after OHCA is in the range of five to 10 variables in many published studies, it is not surprising that regression analysis is frequently used in OHCA research. In fact, four of the six publications included in the systematic review in Chapter 4 used a form of regression analysis, including my own pilot study (Hiltunen *et al.*, 2016; von Vopelius-Feldt, Coulter and Benger, 2015; Yasunaga *et al.*, 2010; Olasveengen *et al.*, 2009). See Figure 7.2 for an example of a logistical regression analysis output from my pilot study to this thesis.

Figure 7.2 Multiple logistic regression of survival following OHCA, including Utstein variables and prehospital critical care team attendance (von Vopelius-Feldt, Coulter and Benger, 2015), with permission from Resuscitation (license number 4300700904166)

	Odds ratio (OR)	95% confidence interval	*p*-Value
Age of patient			
Increment per year, including interaction with first monitored rhythm	0.98	0.96–1.00	$p = 0.02^*$
Location of cardiac arrest			
Nursing home	1 (reference)		
Private residence	1.23	0.41–3.67	$p = 0.71$
Public place	2.75	0.89–8.56	$p = 0.08$
Witnessed cardiac arrest			
Event witnessed by bystander	3.13	1.74–5.65	$p < 0.001^*$
Bystander CPR			
Including interaction with first monitored rhythm	1.88	1.00–3.52	$p = 0.05^*$
Ambulance response time			
Increment per additional minute	0.95	0.89–1.00	$p = 0.04^*$
First monitored rhythm			
Asystole	1 (reference)		
Pulseless electrical activity	10.0	1.70–59.0	$p = 0.01^*$
Ventricular fibrillation or ventricular tachycardia	143	6.08–3356	$p = 0.002^*$
CCT attendance (compared to ALS-paramedic response)	1.54	0.89–2.67	$p = 0.13$

* Statistically significant result ($p < 0.05$).

CPR: Cardiopulmonary resuscitation, CCT: Prehospital critical care team, ALS: Advanced Life Support

There are two concerns regarding the use of regression analysis in this context. The first is the fact that, while the researcher goes through iterative steps to optimise the quality of the regression model, the effects of these changes on the estimated treatment effect studied are visible to the researcher (Holmes, 2014). This can lead to picking the model which best confirms the researcher's bias. In addition, multiple logistic regression models are frequently misspecified unintentionally, based on automated or theoretic processes which do not reflect the nature of the underlying data, resulting in misleading findings (Berk, 2004). The second concern is whether regression analysis can be used to infer causality at all. Guo and

Fraser (2010) demonstrated in simulated datasets that regression analysis resulted in biased over-estimates of treatment effects when treatment assignment was non-ignorable. A review of research publications which used both regression analysis and propensity score methods showed that results were similar, but in 10% of the publications *"the regression method gave a statistically significant association not observed with the propensity score method"* (Shah et al., 2005, p.550).

Propensity score matching combines regression analysis and matching and, in the process, combines the advantages of each method while addressing some of the disadvantages; see Table 7.4 (Holmes, 2014).

Regression analysis is used to predict treatment assignment, rather than outcome, which makes the issue of exact model specification less important (Austin, 2011a). As for traditional regression analysis, the propensity score prediction model can include a large number of variables. The model is then used to predict the probability of each patient receiving the treatment, based on the specified variables. This is called the propensity score, which for every case can take any value between zero (no chance of receiving the treatment) and one (100% chance of receiving the treatment).

The matching of treated and untreated cases is then done on the propensity score, rather than a large number of variables. This significantly improves the efficiency of the matching process while maintaining the assumptions of the counterfactual framework. If propensity score matching works well, relevant covariates C1, C2, C3, … between the treated and untreated group will be balanced between the groups. The difference in outcomes can therefore be assumed to be independent of C1, C2, C3, … and statements about causal inference can be made.

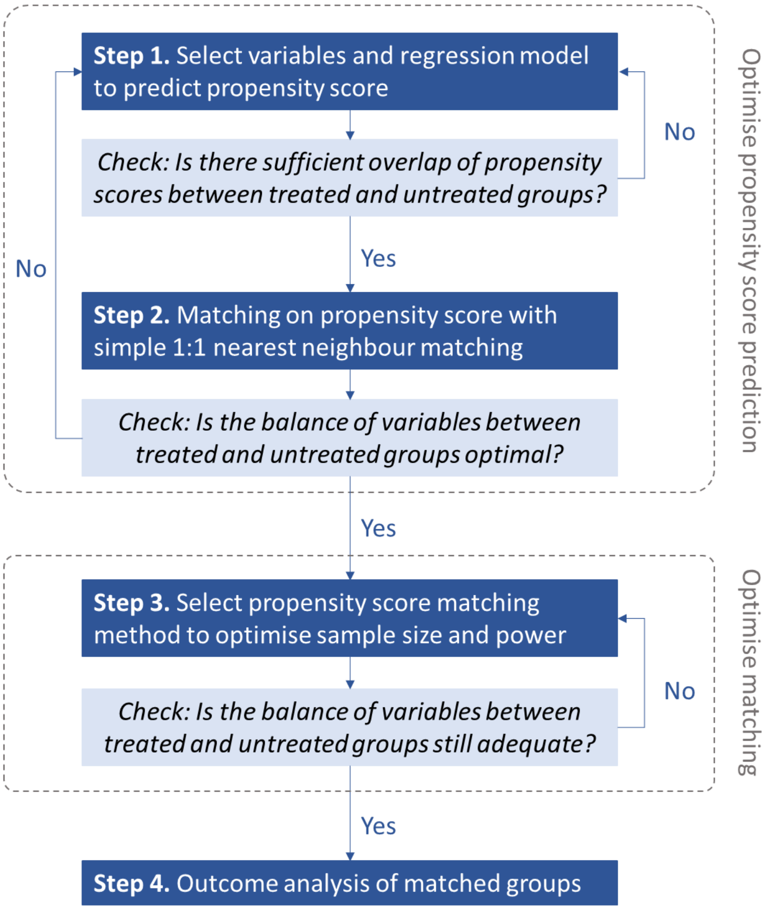
The caveat to this statement is the assumption that all relevant covariates C1, C2, C3, … have been measured accurately and are balanced in the propensity score analysis. Unmeasured variables could still introduce hidden bias and this possibility needs to be carefully assessed by researchers and readers of publications alike. However, a further advantage of propensity score matching is that under certain circumstances, it can partially adjust even for unmeasured confounding (Guo and Fraser, 2010). This process relies on the fact that, in most observational research, covariates with similar effects on the outcome tend to be correlated with each other.

In OHCA, for example, patients with witnessed OHCAs are more likely to receive bystander CPR and have ventricular fibrillation as first cardiac rhythm (Hawkes *et al.*, 2017). All three of these covariates increase a patient's chance of survival following OHCA. In a hypothetical research project where cardiac rhythm had not been measured, propensity score matching would partially balance the rates of witnessed status and bystander CPR and, depending on the strength of the association, the (unmeasured) rates of ventricular fibrillation. I will further address the risk of hidden bias in this analysis in Section 7.5 and in Chapter 9. Of note, while this partial adjustment of unmeasured confounding is frequently described as a feature of propensity score matching, it should, theoretically, also apply to regression analysis and matching (Guo and Fraser, 2010; Hosmer and Lemeshow, 1999).

7.2.7.4 Practical application of propensity score analysis

The method of propensity score matching has been described variably as a three- to six-step process (Holmes, 2014; Guo and Fraser, 2010). I adapted an iterative four-step process with check points as outlined in Figure 7.3, and I will describe each step in detail in this section. All analysis was undertaken in Stata SE (version 14, StataCorp). As all participating ambulance trusts had established different models of prehospital critical care (see Chapter 8 for more detail), I anticipated that the factors predicting prehospital critical care attendance would be unequal for each trust. The iterative steps one to three discussed below were therefore undertaken separately for each trust at first. In the final analysis of step four, I then matched cases of OHCA patients receiving prehospital critical care with those receiving ALS on both the propensity score and the ambulance trust in which the OHCA occurred.

Figure 7.3 Stepwise approach to propensity score matching, adapted from Guo and Fraser (2010) and Holmes (2014)



Step 1. I used cross-tabulation and the chi-square or t-test statistics (for categorical and continuous variables, respectively) as well as logistic regression to assess if the Utstein variables summarised in Table 7.2 were associated with the treatment of prehospital critical care attendance and/or the primary outcome of survival to hospital discharge.

To deal with likely non-linearity between continuous variables (such as age or ambulance response times) and the effect on both the intervention and the outcome, I converted all continuous variables into categorical variables. The cut off points for categories were chosen based on clinical and practical reasons.

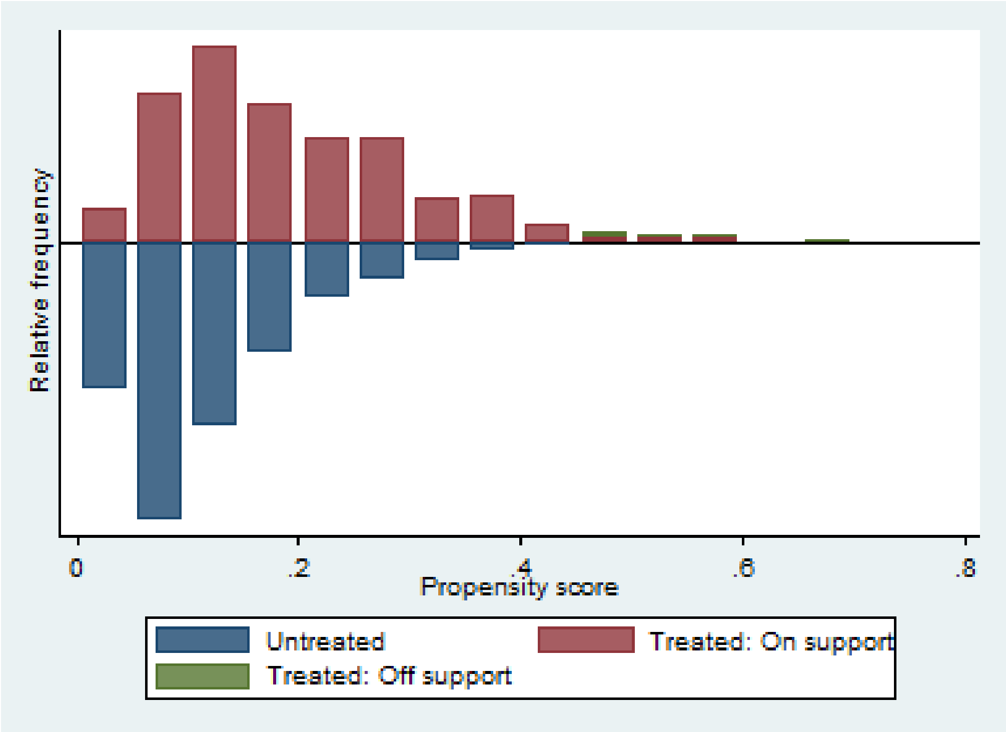
To predict the propensity score, I first used a multiple logistic regression model which included all variables undertook a backward stepwise selection process guided by the results of the cross-tabulation and logistic regression of Utstein variables, a process suggested by Rosenbaum and Rubin (1985). Backward stepwise regression starts with a model which includes all relevant variables which then get removed from the model one at a time (Guo and Fraser, 2010). I removed variables in the following order, using a high threshold for p-values of associations (p<0.2)

- No association of variable with prehospital critical care or survival
- Variable associated with prehospital critical care but not with survival
- Variable associated with survival but not with prehospital critical care

Variables which were associated with prehospital critical care attendance and survival were not removed from the propensity score prediction model, as this would have been very unlikely to improve the balancing properties of the propensity score matching process (Holmes, 2014).

For each model, the first check following the calculation of the propensity score was to assure that there was sufficient overlap in the distributions of propensity score between the prehospital critical care group and the Advanced Life Support group. Insufficient overlap indicates the possibility that the two groups are not actually comparable and results in large numbers of both treated and untreated cases being lost in the matching process (Austin, 2011a). All tested models described above showed sufficient overlap in propensity scores at this checkpoint and advanced to step 2. See Figure 7.4 for a representative example of propensity score distributions with sufficient overlap.

Figure 7.4 Example of propensity score distribution between Advanced Life Support and prehospital critical care cases

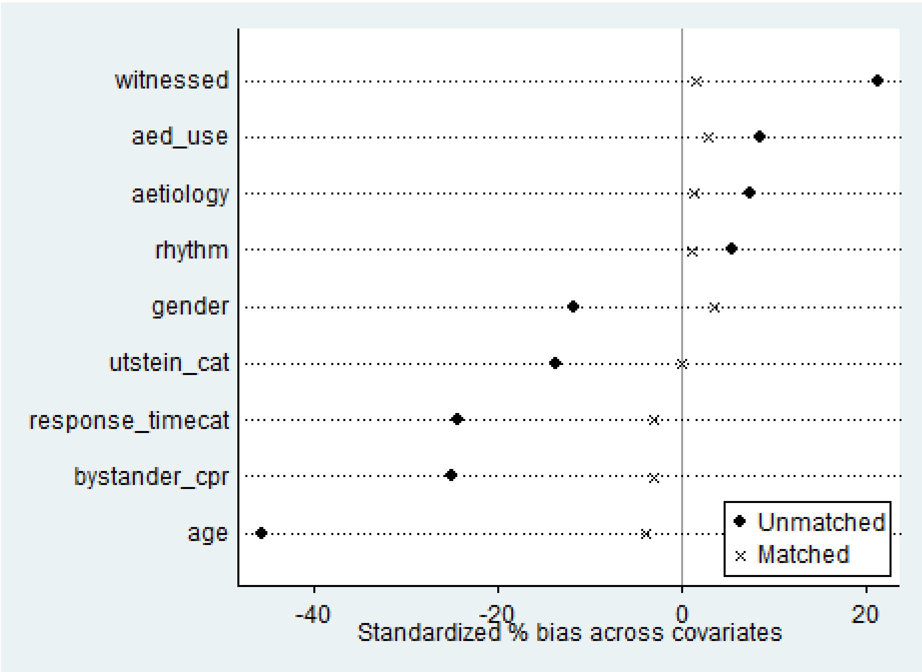


Untreated = ALS care, Treated = Prehospital critical care. Treated: Off support = Prehospital critical care cases without ALS cases with matching propensity score.

Step 2. The best method of assessing whether propensity score calculation of a given model were successful is still debated (Austin, 2009). A number of diagnostic tests are available for logistic regression models but are considered largely irrelevant in the context of propensity score matching (Starks and Garrido, 2014; Guo and Fraser, 2010). However, most authors agree that the key feature of a successful propensity score calculation is the balance of covariates between treated and untreated groups after matching (Holmes, 2014; Guo and Fraser, 2010; Dehejia and Wahba, 2002).

Austin (2009) recommends using the reduction in standardised differences of the covariates before and after matching as a measure of successful balancing. I therefore compared the standardised difference between covariates for every model using simple 1:1 nearest neighbour matching, using a calliper of 0.2 * the standard deviation of the propensity score (Guo and Fraser, 2010). The calliper determines the maximal distance between two propensity scores which is considered a match. Bigger callipers result in easier matching but less precision and increasing risk of covariate imbalance after matching. The formula of 0.2 * the standard deviation of the propensity score is recommended as a reasonable compromise between finding matches and matching precision (Starks and Garrido, 2014; Guo and Fraser, 2010). See Figure 7.5 for a representative graphic example of covariate balance before and after matching of prehospital and critical care cases of OHCA.

Figure 7.5 Representative graphic example of covariate balance before and after a trial of matching on propensity score in Trust Alpha data sample



Step 3. For the model which demonstrated the best balance of covariates after 1:1 nearest neighbour matching, I evaluated a set of further matching procedures. The aim of this step was to maximise the sample size and power after matching, while monitoring for any significant increase in covariate imbalance and risk of bias. The matching methods evaluated were

- 1:n nearest neighbour calliper matching (greedy algorithm) with a maximum of 1:2 matching
- 1:n nearest neighbour calliper matching (greedy algorithm) with a maximum of 1:3 matching
- 1:n nearest neighbour calliper matching (greedy algorithm) with a maximum of 1:4 matching
- Mahalanobis matching within a given calliper (Guo and Fraser, 2010)

All models were started off with callipers of 0.2*SD of the propensity score. If covariate imbalance was too large, smaller callipers of 0.15 or 0.1*SD were trialled. However, previous research has shown that the calliper size has only minimal impact on balancing properties if most of the covariates are not continuous, as is the case in this data (Austin, 2011b). Mahalanobis matching resulted in poorly balanced groups, so the final matching process was nearest neighbour matching with a 1:n ratio.

Step 4. After optimising propensity score prediction and the matching process in steps 1 to 3, I used the final models of propensity score matching selected from this process to match patients on the propensity score and the ambulance trust in which the OHCA occurred. Analysis of this matched data is discussed in the next section.

7.2.8 Outcome analysis

As described in the previous section, one of the advantages of propensity score matching is that adjustment for confounding occurs at the design stage of the data, rather than at the stage of analysis (Guo and Fraser, 2010). As such, analysis of the outcomes of interest, survival to hospital discharge (primary) and survival to hospital arrival (secondary) can be undertaken independently from the process of propensity score matching. Nevertheless, important aspects resulting from this process need to be considered.

Propensity score matching reduced the cohort of OHCA patients receiving ALS care to those patients with similar baseline characteristics (Utstein variables) to the group of patients who received prehospital critical care. Any treatment effect calculated from these two matched cohorts therefore represents the average treatment effect on the treated population (ATT), rather than the treatment effect one would see if the whole group of OHCA patients was to receive prehospital critical care (Holmes, 2014). This is an important consideration when attempting to generalise the results of this analysis.

It has been argued that, if propensity score matching resulted in sufficient balance of confounding variables, the treatment effect (ATT) can be calculated by simply comparing the proportions of the outcome between the matched groups. If the groups only differ in regard to their treatment allocation, the propensity score matching has successfully replicated an RCT and the treatment effect can therefore be estimated the same way. However, some differences to RCTs remain - when estimating the variance and statistical significance (95% confidence intervals and p-values), and when the balance of covariates after matching is less than perfect.

The choice of statistical tests needs to reflect the matched nature of the sample, such as for example the frequently used McNemar test which is appropriate for 1:1 matching. For 1:n matched samples, conditional logistic regression is recommended (Austin, 2011c). The advantage of using conditional logistic regression for the outcome analysis is that, in the case of remaining imbalance of measured confounders, these can be included in the conditional logistic regression model and the resulting odds ratio is adjusted for this imbalance (Hosmer and Lemeshow, 1999). Nguyen *et al.* (2017) recommend the use of conditional logistic regression if the imbalance in prognostic factors exceed a standardised difference of 10%.

Given the conditions of 1:n matching and a high likelihood of some imbalance after propensity score matching (based on the trial runs described in Section 7.2.7.4), I chose to use conditional logistic regression for the outcome analysis of both primary and secondary outcome.

7.2.9 Sample size estimation

Provisional data for Trust Alpha for March 2015 had shown that resuscitation for OHCA was commenced by prehospital providers in approximately 100 cases during the month. Rates of survival across the four ambulance trusts averaged 7.5%. I estimated that after application of inclusion and exclusion criteria, I would be able to include 6,000 patients, of which approximately 600 would have been attended by a prehospital critical care provider or team. This would have allowed me to detect an absolute improvement in the primary outcome of survival to hospital discharge of approximately 4% with a power of 0.8 and alpha 0.05, assuming one-to-two matching and a survival rate of 7.5% in the control group. This is in keeping with the minimal economically important difference I calculated in the previous chapter as well as the minimal clinically important difference (MCID) described in previous research (Nichol *et al.*, 2016). Nichol *et al.* (2016) also calculated an associated estimated sample size for the MCID, which was 1,683 cases of OHCA, assuming a one-to-one allocation to intervention and control groups.

7.2.10 Subgroup analysis

I included a subgroup analysis of patients with witnessed OHCA due to a shockable cardiac rhythm (VF or pulseless ventricular tachycardia). These patients are also referred to as the Utstein comparator group in OHCA research, as the working group responsible for the OHCA Utstein criteria recommends reporting outcomes in this subgroup (Perkins *et al.*, 2015a). It is thought that analysing the outcomes of patients with witnessed OHCA with initial shockable rhythm is a more robust way of comparing healthcare systems serving different populations, as survival is determined more by the healthcare interventions delivered and less by population-specific confounders (Perkins *et al.*, 2015a; Nishiyama *et al.*, 2014).

7.2.11 Intention-to-treat or as-treated analysis

As discussed in Chapter 4, prehospital critical care is commonly provided as second or third tier response to OHCA, including the ambulance trusts participating in this research. In Chapter 4, I describe how this tiered response can introduce selection bias, if prehospital critical care providers are stood down from resuscitations with very low likelihood of success. None of the studies included in the systematic review provided clear data on the possibly significant effects of what is essentially an issue of intention-to-treat vs as-treated analysis.

While all participating prehospital critical care services operate slightly different clinical and dispatch models (see also Chapter 8), there are four potential scenarios of prehospital critical care dispatch for OHCA within the participating services; see Box 7.1. Table 7.5 describes how these scenarios are allocated to the study groups for either intention-to-treat or as-treated analysis.

Box 7.1 Four potential scenarios of dispatch of prehospital critical care services for out-of-hospital cardiac arrest

1. ALS care. The OHCA is attended by ALS paramedics only, with the prehospital critical care service not involved at all. This can be due to unavailability of the critical care service or patient characteristics available at the time of the 999 call.

2. Primary dispatch. The prehospital critical care service is dispatched to the OHCA based on the information available at the time of 999 call.

3. Secondary dispatch. The OHCA is initially only attended by ALS paramedics, the critical care service is not activated, as in scenario 1. However, once the ALS paramedics are on scene and have assessed the patient, they request the prehospital critical care service. This is generally due to new information gained which wasn't available at the time of the 999 call. To my knowledge, there is no published research on this, from personal experience, common reasons are either a futile resuscitation for which the ALS paramedics require a more senior provider to allow termination of resuscitation; or an unexpectedly successful resuscitation with the patient then requiring prehospital critical care interventions.

4. Stand-down. The prehospital critical care service is dispatched to the OHCA based on the information available at the time of 999 call, as in scenario 2. However, ALS paramedics arriving on scene first decide that the critical care team is not required. From experience, reasons for stand-downs are because the resuscitation is deemed futile once assessed by ALS paramedics; or the patient has been resuscitated so quickly (generally from OHCA with a shockable rhythm) that they are conscious and do not require prehospital critical care.

ALS: Advanced Life Support, OHCA: Out-of-hospital cardiac arrest

Table 7.5 Inclusion of patients in either Advanced Life Support or prehospital critical care group, according to intention-to-treat or as-treated analysis

Analysis	ALS group	Prehospital critical care group
Intention-to-treat	Scenario 1 and 3	Scenario 2 and 4
As-treated	Scenario 1 and 4	Scenario 2 and 3

ALS: Advanced Life Support

It is important to note that the dispatch mechanisms leading to scenario 1 or 2 (ALS care or primary dispatch of a prehospital critical care provider, respectively) are relatively straightforward, largely based on Utstein variables and should be accounted for in the process of propensity score matching.

Scenario 3 and 4 (secondary dispatch or stand-down of a prehospital critical care service, respectively) are somewhat more complicated. Both include a combination of patients with either very high or very low chances of survival following OHCA, which are likely based on variables not recorded in the OHCAO dataset. Without previous data on these groups, predicting the influence of scenario 3 or 4 on the outcome is extremely difficult. In RCTs, as-treated analysis frequently results in unduly optimistic estimates of treatment effects, as patients who respond poorly to the intervention are more likely to drop out of the study (Shrier *et al.*, 2014). While in these situations, intention-to-treat is the preferred analysis strategy to ensure unbiased estimates of effectiveness, no such guidance exists for the situation faced here.

In keeping with a pragmatic approach, I therefore decided that as-treated analysis would be the primary analysis, as it reflects actual practice. To assess the effect of the scenarios described above on outcomes, I will present survival rates for each scenario. In addition, I will present the results of a secondary analysis, which will exclude all cases where further information from the scene changed dispatch of prehospital critical care (secondary dispatch and stand-downs).

7.2.12 Ethics and consent

The research protocol underlying this thesis was reviewed and approved by the Sheffield National Research Ethics Service Committee, York and Humber on 29 July 2016, reference number 16/YH/0300. The key ethical question for the research in this chapter was the collection of patient data without consent. The research ethics committee (REC) was satisfied that

a. Gaining consent was not a realistic option in a patient population with an immediate mortality rate of approximately 90%
b. The data collected would not allow me to identify individual patients

The REC therefore agreed that patient consent did not need to be obtained. However, following strict data management procedures was deemed important to avoid either loss or unintended disclosure of data; see next section.

7.2.13 Data management

Data was transferred from participating ambulance trust research and development departments via my NHSmail account j.vopelius@nhs.net. The email service is accredited to *"Government Official Sensitive"* status and has been approved by the Department of Health for sharing patient identifiable or sensitive information (NHS Digital, 2018a). Data was transferred in Excel (Microsoft) spreadsheets. I stored all data on a password-protected PC in a secure office at the University of the West of England (UWE) and used a monthly backup schedule using the UWE network drive, in accordance with UWE data protection requirements (University of the West of England, 2015).

7.3 Results

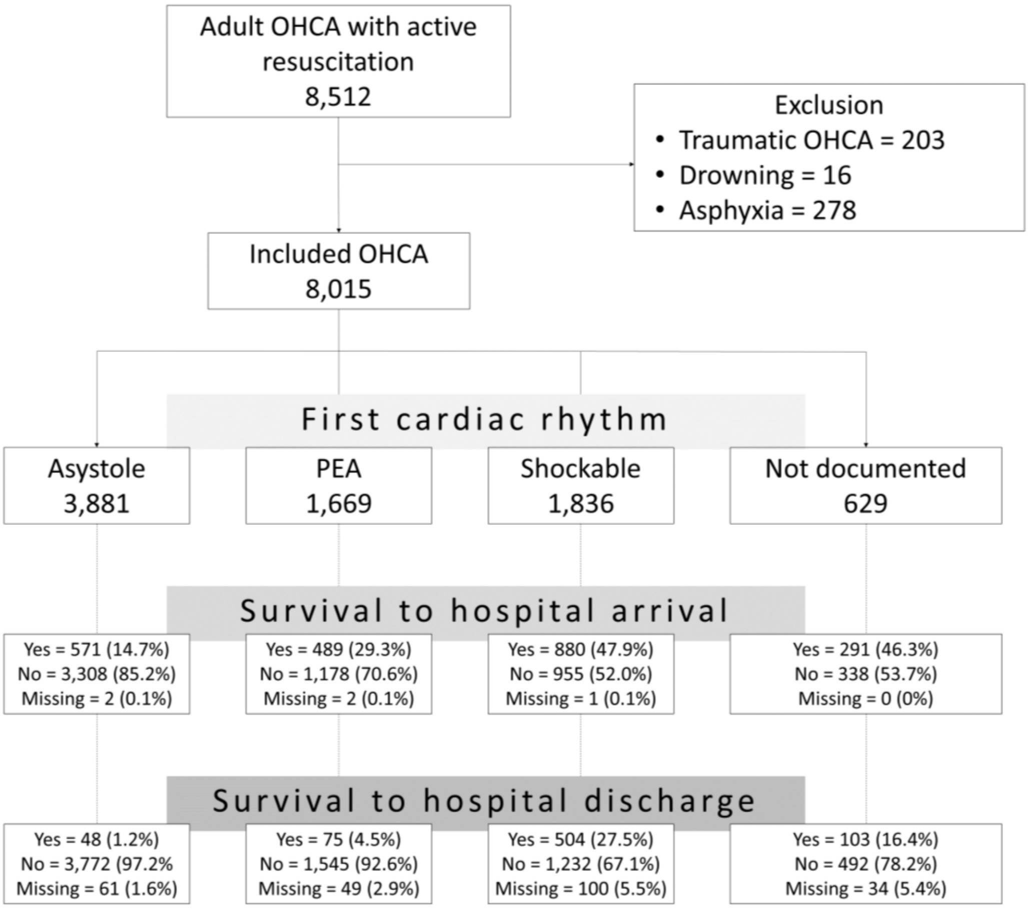
7.3.1 Participating ambulance trusts

All four ambulance trusts successfully collected and transferred data from their critical care services directly to me. However, at the time of writing this thesis (May 2018), of the four participating ambulance trusts, only Trust Alpha and Trust Beta have submitted their data to the OHCAO database for the study period. The analysis presented in this chapter and Chapter 8 is therefore solely based on data from these two ambulance trusts and the corresponding prehospital critical care services. The relevant OHCAO data from Trust Charlie and Trust Delta is expected to be transferred in October 2018 at the earliest. I will repeat the relevant analyses presented in both chapters, once the final data has been transferred and cleaned, and submit the final analysis for peer review and publication.

7.3.2 Demographics of out-of-hospital cardiac arrest

Between September 2016 and October 2017, there were 8,512 cases of adult OHCA, for which resuscitation was undertaken, in Trust Alpha and Trust Beta. After application of exclusion criteria, 8,015 cases of OHCA remained for analysis, with an overall survival rate of 9.1%. Figure 7.6 gives an overview of exclusion criteria, first presenting cardiac rhythm during OHCA, missing data rates and outcomes, in the recommended Utstein flow chart.

Figure 7.6 Flowchart of cases of out-of-hospital cardiac arrest included in the analysis



OHCA: Out-of-hospital cardiac arrest, PEA: Pulseless electrical activity

7.3.3 Prehospital critical care and Advanced Life Support - imbalance of prognostic factors

Of the 8,015 patients with OHCA, 866 (10.9%) received care from one or more prehospital critical care provider. Table 7.6 gives an overview of the distribution of patient demographics, prognostic factors and completeness of data for both treatment groups. As expected, positive prognostic factors in the prehospital critical care group were all significantly more frequent in the prehospital critical care group when compared to the ALS care group.

Table 7.6 Patient demographics and prognostic factors in out-of-hospital cardiac arrest cases receiving Advanced Life Support and prehospital critical care

	ALS care (n=7,149)	**Critical care** (n=866)	**Statistical significance***
Age (median, IQR)	74 (62 – 84)	67 (54 – 76)	p<0.001
Missing data	*58 (0.8%)*	*13 (1.5%)*	
Gender (male)	4,549 (63.9%)	611 (70.6%)	p<0.001
Missing data	*24 (0.3%)*	*1 (0.1%)*	
Location of OHCA			
Public area	758 (10.6%)	225 (26.0%)	p<0.001
Private residence	3,754 (52.5%)	536 (61.9%)	
Assisted living	274 (3.8%)	12 (1.4%)	
Other	324 (4.5%)	22 (2.5%)	
Missing data	*2,039 (28.5%)*	*71 (8.2%)*	
Aetiology			
Presumed cardiac	6,486 (90.7%)	821 (94.8%)	p<0.001
Drug overdose	122 (1.7%)	22 (2.5%)	
Exsanguination	4 (0.1%)	0 (0%)	
Other	435 (6.1%)	8 (0.9%)	
Missing data	*102 (1.4%)*	*15 (1.7%)*	
Event witnessed			
Bystander	3,506 (49.0%)	540 (62.4%)	p<0.001
EMS	1,225 (17.1%)	68 (7.9%)	
Not witnessed	2,390 (33.4%)	251 (29.0%)	
Missing data	*28 (0.4%)*	*7 (0.8%)*	
Cardiac rhythm			
Shockable	1,531 (21.4%)	305 (35.2%)	p<0.001
PEA	1,539 (21.5%)	130 (15.0%)	
Asystole	3,542 (49.6%)	339 (39.2%)	
Missing data	*537 (7.5%)*	*92 (10.6%)*	
Bystander CPR**			
Yes	3,986 (67.3%)	620 (77.7%)	p<0.001
No	1,925 (32.5%)	169 (21.2%)	
Missing data	*13 (0.2%)*	*9 (1.0%)*	
AED used	233 (3.3%)	54 (6.2%)	p<0.001
Missing data	-	-	
EMS response time			
(median, IQR)	7.2 min (4.8 – 11.0)	8.8 min (5.8 – 13.7)	p<0.001
Missing (percent)	*8 (0.1%)*	-	

**Wilcoxon Rank Sum test for non-normally distributed data, Pearson's chi-square test for categorical data ** Excludes EMS-witnessed OHCAs*
ALS: Advanced Life Support, IQR: Interquartile range, OHCA: Out-of-hospital cardiac arrest, EMS: Emergency Medical Services, PEA: Pulseless electrical activity, CPR: Cardiopulmonary resuscitation, AED: Automated external defibrillator

7.3.4 Unadjusted outcomes

The unadjusted rates for the primary outcome of survival to hospital discharge were 8.7% and 12.8% in the ALS and prehospital critical care group (p<0.001). The unadjusted rates of survival to hospital arrival after OHCA were 26.8% and 36.4% for the ALS group and the prehospital critical care group, respectively (p<0.001). Rates of missing data were 3.2% and 2.2% for survival to hospital discharge and 0.1% and 0% for survival to hospital arrival for the ALS group and prehospital critical care group, respectively. Given the imbalance of prognostic factors demonstrated in Table 7.6, neither the primary nor secondary outcome should be interpreted without appropriate adjustment.

The following sections describe the primary analysis, subgroup analysis and two sensitivity analyses, using propensity score matching. I will describe the propensity score matching process in more detail for the primary analysis but to avoid repetition, I will only focus on key points and results for the other analyses. Finally, in Section 7.3.7, I will present an overview of the results of all analyses.

7.3.5 Primary analysis – propensity score matching of complete cases, as treated

After excluding all cases with incomplete relevant data, 5,123 cases of OHCA remained for complete case analysis. Of these, 665 received prehospital critical care. The iterative steps described in Section 7.2.7.4 needed to be slightly adapted. First, to address the problem of likely non-linearity between continuous variables and the outcome (treatment by a prehospital critical care provider) in multiple logistic regression (MLR), I transformed continuous variables into categorical variables (Hosmer and Lemeshow, 1999). Second, matching OHCAs with prehospital critical care to OHCAs with ALS care at varying ratios had unpredictable effects on the balance of covariates which could be achieved. I therefore tested each potential MLR model, used to predict the propensity score, with a number of matching strategies, to identify the overall optimal propensity score matching strategy. Details of this process are given in Appendix C2. The propensity score matching process which resulted in the most optimal balance between covariates included the variables below in the MLR model which predicted the propensity score for attendance of a critical care team:

- Age of patient
- Gender
- Utstein location of OHCA

- Aetiology of OHCA
- Witnessed event
- Bystander CPR
- EMS response time
- First recorded cardiac rhythm

The optimal matching strategy in terms of covariate balance but also power was 1:3 matching, where each OHCA patient with prehospital critical care attendance was matched to a maximum of three patients with ALS care. Appendix C3 provides an example of the code written by myself in Stata SE (version 14, StataCorp) to undertake 1:3 propensity score matching without replacement. Table 7.7 shows how many OHCAs with ALS care were matched to each OHCA with prehospital critical care.

Table 7.7 Number of matched and unmatched out-of-hospital cardiac arrest cases in the prehospital critical care and Advanced Life Support groups

Number of OHCAs with prehospital critical care	**Ratio of match**	**Number of OHCAs with ALS care**
7 (1.1%)	Not matched	3,276 (64.9%)
30 (4.5%)	1:1	30 (0.6%)
67 (10.08%)	1:2	134 (2.6%)
561 (84.4%)	1:3	1,683 (32.9%)
Total matched		**Total matched**
658 (98.9%)		1,847 (36.1%)

OHCA: Out-of-hospital cardiac arrest, ALS: Advanced Life Support

Reducing the calliper to less than 0.2 * the standard deviation of the propensity score did not significantly improve covariate balance but reduced the number of matches (data not shown). Table 7.8 shows the balance of prognostic factors achieved through the optimised propensity score matching process described above.

Table 7.8 Patient demographics and prognostic factors after 1:3 propensity score matching (complete case analysis)

	ALS care (n=1,847)	**Critical care** (n=658)	***Standardised difference****
Age (median, IQR)	69 (57 – 77)	68 (55 – 77)	*9.1%*
Gender (male)	1,302 (70.5%)	457 (69.5%)	*2.3%*
Location of OHCA			
Public area	392 (21.2%)	162 (24.6%)	*12.0%*
Private residence	1,379 (74.6%)	464 (70.5%)	
Assisted living	16 (0.9%)	12 (1.8%)	
Other	60 (3.3%)	20 (3.0%)	
Aetiology			
Presumed cardiac	1,802 (97.6%)	639 (97.1%)	*2.8%*
Drug overdose	45 (2.4%)	19 (2.9%)	
Exsanguination	-	-	
Other	-	-	
Event witnessed			
Bystander	1,106 (59.9%)	414 (62.9%)	*7.1%*
EMS	185 (10.0%)	55 (8.4%)	
Not witnessed	556 (30.1%)	189 (28.7%)	
Cardiac rhythm			
Shockable	668 (36.2%)	254 (38.6%)	*5.1%*
PEA	310 (16.8%)	108 (16.4%)	
Asystole	869 (47.1%)	296 (45.0%)	
Bystander CPR**			
Yes	1,282 (77.1%)	466 (77.3%)	*0.5%*
No	380 (22.9%)	137 (22.7%)	
AED used	48 (2.6%)	22 (3.3%)	*4.3%*
EMS response time (median, IQR)	8.1 min (5.3 – 13.0)	8.8 min (5.7 – 13.7)	*9.2%*
Survival to hospital discharge	**220 (11.9%)**	**78 (11.9%)**	
Survival to hospital arrival	**511 (27.7%)**	**226 (34.4%)**	

** Values of 10% or less are considered to indicate a good balance for a given variable (Austin, 2009)*
*** Excludes EMS-witnessed OHCAs*
ALS: Advanced Life Support, IQR: Interquartile range, OHCA: Out-of-hospital cardiac arrest, EMS: Emergency Medical Services, PEA: Pulseless electrical activity, CPR: Cardiopulmonary resuscitation, AED: Automated external defibrillator

By using propensity score matching, the matched ALS care group in Table 7.8 has been made more similar to the prehospital critical care group, resulting in more positive prognostic factors when compared to the original ALS cohort described in Table 7.6. As a result, the adjusted rates of survival to hospital arrival and survival to hospital discharge of the ALS care group in Table 7.8 are higher than the unadjusted outcomes described in the previous section.

Given the overall good balance of Utstein variables achieved through propensity score matching, the rates of survival to hospital arrival and survival to hospital discharge presented in Table 7.8 can be compared directly between the groups, to estimate the size of the treatment effect on the treated patients. In this case, the absolute treatment effect for the primary outcome of survival to hospital discharge is 0%, while the absolute treatment effect for the secondary outcome of survival to hospital arrival is 6.7%.

To eliminate the effect of any residual imbalance and allow for testing of statistical significance of the difference in rates of outcomes, I undertook a conditional logistic regression analysis, which included all variables listed in Table 7.8 as well as the time of the 999 call. The conditional logistic regression of the matched groups resulted in an odd ratio (OR) of 1.06 (95%CI 0.75 – 1.49) for the primary outcome of survival to hospital discharge and an OR of 1.39 (95%CI 1.10 – 1.75) for the secondary outcome of survival to hospital arrival, with a p-value of 0.75 and of 0.005, respectively. In other words, in this a priori defined primary analysis, prehospital critical care had no significant association with the primary outcome of survival to hospital discharge, but a significant association with the secondary outcome of survival to hospital arrival.

7.3.6 Subgroup analysis - bystander-witnessed out-of-hospital cardiac arrest with shockable rhythm

Analysis of outcomes in the subgroup of patients with bystander-witnessed, shockable OHCA was determined a priori. Results in this group of patients, also referred to as the Utstein comparator group, can be used to assess the effectiveness of pre-hospital healthcare systems for OHCA, independent of changes in the population (the frequency of asystole and PEA has increased over recent years). They also allow benchmarking and comparison between EMS systems operating in different countries or regions.

Table 7.9 Patient demographics and prognostic factors in bystander-witnessed out-of-hospital cardiac arrest with initial shockable rhythm

	ALS care (n=935)	**Critical care** (n=225)	**Statistical significance***
Age (median, IQR)	70 (60 – 79)	65 (53 – 74)	p<0.001
Missing data	*9 (1.0%)*	*4 (1.8%)*	
Gender (male)	734 (78.8%)	186 (82.7%)	p>0.1
Missing data	*3 (0.3%)*	-	
Location of OHCA			
Public area	222 (23.7%)	82 (36.4%)	p<0.001
Private residence	449 (48.0%)	118 (52.4%)	
Assisted living	11 (1.2%)	2 (0.9%)	
Other	13 (1.4%)	1 (0.4%)	
Missing data	*240 (25.7%)*	*22 (9.8%)*	
Aetiology			
Presumed cardiac	903 (96.6%)	224 (99.6%)	p>0.05
Drug overdose	6 (0.6%)	1 (0.4%)	
Other	20 (2.1%)	-	
Missing data	*6 (0.6%)*	-	
Bystander CPR			
Yes	727 (77.8%)	190 (84.4%)	p<0.05
No	205 (21.9%)	34 (15.1%)	
Missing data	*3 (0.3%)*	*1 (0.4%)*	
AED used	54 (5.8%)	18 (8.0%)	p>0.1
Missing data	-	-	
EMS response time			
(median, IQR)	6.7 min (4.5 – 9.6)	8.2 min (5.4 – 12.0)	p<0.001
Missing (percent)	-	-	

ALS: Advanced Life Support, IQR: Interquartile range, OHCA: Out-of-hospital cardiac arrest, EMS: Emergency Medical Services, PEA: Pulseless electrical activity, CPR: Cardiopulmonary resuscitation, AED: Automated external defibrillator

The unadjusted rates of survival to hospital discharge (primary outcome) after bystander-witnessed OHCA with a shockable rhythm were 24.8% and 29.4% in the ALS and prehospital critical care group, respectively (p=0.006). Rates of survival to hospital arrival (secondary outcome) were 45.5% and 56.9% for the ALS group and the prehospital critical care group, respectively (p=0.008).

I undertook a complete case analysis and propensity score matching as described for the primary analysis. After exclusion of cases with missing data, propensity score matching resulted in 629 bystander-witnessed OHCAs with shockable rhythm, 188 of which received prehospital critical care. The OR for survival to hospital discharge and survival to hospital arrival when receiving prehospital critical care were 1.20 (0.76- 1.90, p=0.44) and 1.56 (95%CI 1.01 – 2.40, p=0.04), respectively.

7.3.7 Sensitivity analyses

To assess the robustness of the results of the primary analysis, I undertook two sensitivity analyses, one of which was defined a priori (primary-dispatch-only analysis), while the need for a sensitivity analysis using multiple imputation only became clear once I started analysis of data from the OHCAO Registry. Both analyses were undertaken with the same logistic regression model to predict propensity score matching and the same 1:3 matching process as the primary analysis. This section therefore focuses on the results of the analyses only.

7.3.7.1 Sensitivity analysis - primary dispatch of prehospital critical care only

As discussed in Section 7.2.9, the decision to dispatch a prehospital critical care team can be complex. Not infrequently, this decision might be reversed once further information is available from the scene of the OHCA; see Section 7.2.9 for further explanation. While I decided on an as-treated analysis as primary analysis, the effect of the scenarios of primary dispatch, secondary dispatch or stand-down of prehospital critical care teams was difficult to predict a priori. Table 7.10 displays the unadjusted survival rates for each possible scenario of prehospital care for OHCA.

Table 7.10 Unadjusted rates of survival to hospital discharge after out-of-hospital cardiac arrest, by dispatch category of prehospital critical care teams (missing data not shown)

Level of care received and mode of dispatch of prehospital critical care team	**Rates of survival to hospital discharge**	
ALS care only (n=4,365)	8.4%	P<0.001 for all-group comparison
Primary dispatch of critical care team (n=464)	9.7%	
Secondary dispatch of critical care team (n=191)	15.7%	
Stand-down of activated critical care team (n=70)	5.7%	

ALS: Advanced Life Support

Patients for which the prehospital critical care team was dispatched only after request by an ALS crew had higher survival rates then the general OHCA population. Conversely, stand-downs of prehospital critical care teams were associated with lower survival rates. Using the same steps of propensity score matching as for the primary analysis, this secondary analysis only compared primary dispatch of prehospital critical care team to OHCA with primary dispatch of ALS paramedics. Secondary dispatch and stand-downs of critical care teams were excluded. After propensity score matching, 458 cases of OHCA receiving prehospital critical care were compared to 1,297 cases of OHCA with ALS care. The OR for survival to hospital discharge was 0.87 (95%CI 0.56 – 1.40, p=0.61) and the OR for survival to hospital arrival was 1.28 (95%CI 0.97 – 1.69, p=0.08).

7.3.7.2 Sensitivity analysis - multiple imputation

As demonstrated in Table 7.6, the OHCAO dataset had a significant number of missing variables. The most notable were Utstein location of OHCA (26.2% missing), first recorded cardiac rhythm (7.9% missing) and survival to hospital discharge (3% missing). Overall, exclusion of cases with missing data led to a loss of 2,893 of a total of 8,015 cases of OHCA (36.1%).

Figure 7.6 and Table 7.6 also demonstrate that data is not missing completely at random. Survival data is missing more frequently in OHCAs with a shockable cardiac rhythm and if the data on cardiac rhythm is also missing. Utstein location data, on the other hand, is much more frequently missing in the ALS group, when compared to the prehospital critical care group. The fact that data is not missing completely at random introduces the possibility of bias in the primary complete case analysis undertaken above (Pedersen *et al.*, 2017; Newgard, 2006). Multiple imputation of missing data is considered to be the adjustment method of choice for data not missing completely at random (Kaambwa, Bryan and Billingham, 2012).

To assess if the exclusion of cases with missing data might have biased the primary analysis, I added a post-hoc secondary analysis of a dataset where missing values were replaced with multiple imputations. In short, I used multiple logistic regression to impute the likely values for missing data for each OHCA in the dataset, based on the observed variables of the given OHCA case (Groenwold *et al.*, 2012). This process is repeated multiple times, with slightly different results for each variable, creating multiple datasets.

The current recommendation for the number of imputations required is based on the fraction of information missing, which is equal to or less than the percentage of missing values in the whole dataset (2.9% in this case) (Rubin and Schenker, 1991). As the exact number of imputations is an ongoing debate (Graham, Olchowski and Gilreath, 2007), I chose a conservative number of 10 imputations (Hayati Rezvan, Lee and Simpson, 2015). I then undertook the propensity score matching process selected for the primary analysis for each dataset. Table 7.11 gives an example of 10 imputations for two cases with missing cardiac rhythm and survival, respectively.

Table 7.11 Example of two cases of out-of-hospital cardiac arrest with multiple imputations for missing cardiac rhythm and survival to hospital discharge data, respectively

	76 year-old female, bystander-witnessed OHCA at home, no bystander CPR, no AED use. Ambulance response time 7min. Survived to hospital but not to hospital discharge. Initial cardiac rhythm not recorded.	*70 year-old female, unwitnessed OHCA in public area, bystander CPR, no AED use. EMS response time 3min. Initial shockable cardiac rhythm. Survived to hospital but survival to hospital discharge data is missing.*
Imputed dataset number	**Imputed cardiac rhythm**	**Imputed outcome**
1	Asystole	In-hospital death
2	PEA	Survival to hospital discharge
3	Asystole	Survival to hospital discharge
4	Asystole	In-hospital death
5	Asystole	In-hospital death
6	VF/pulseless VT	Survival to hospital discharge
7	Asystole	In-hospital death
8	Asystole	In-hospital death
9	VF/pulseless VT	Survival to hospital discharge
10	VF/pulseless VT	In-hospital death

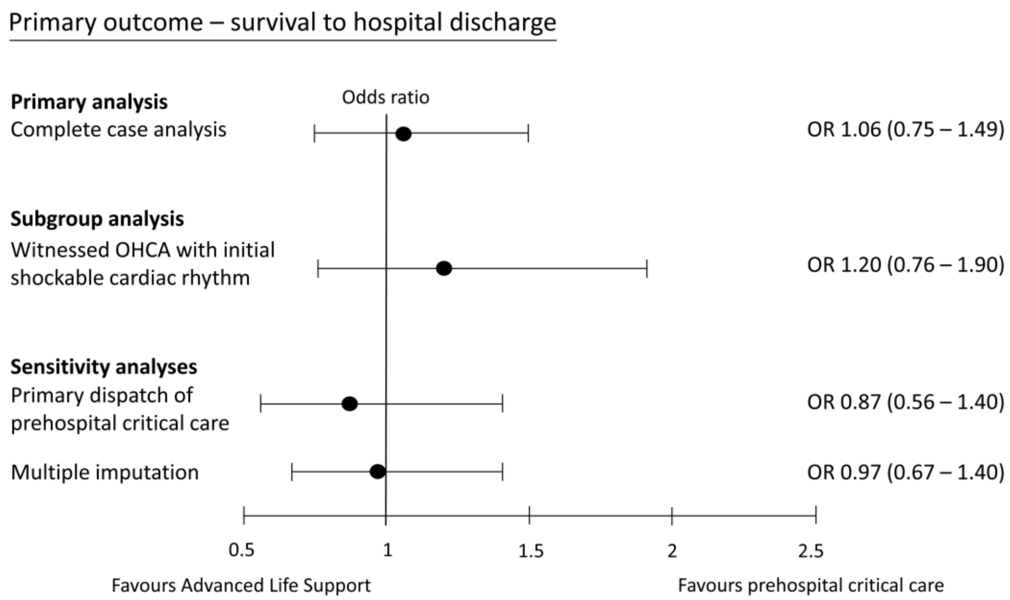
OHCA: Out-of-hospital cardiac arrest, CPR: Cardiopulmonary resuscitation, AED: Automated external defibrillator, PEA: Pulseless electrical activity, VF: Ventricular fibrillation, VT: Ventricular tachycardia

The result of propensity score matching of the multiply imputed datasets are 10 distinct ORs and 10 95% confidence intervals. These ORs and confidence intervals were combined using Rubin's Rule for analysis of multiple imputation data, after log transformation to account for the non-normal distribution of ORs (Miles, 2015). The results of the propensity score analysis of the multiple imputation datasets was a comparison of 848 cases of OHCA with prehospital care and 2,363 cases of OHCA with ALS care. ORs for primary and secondary outcome of survival to hospital discharge and survival to hospital arrival were 0.97 (95%CI 0.67 – 1.40) and 1.49 (95%CI 1.08 – 2.04), respectively.

7.3.8 Overview of results from primary, subgroup and sensitivity analyses

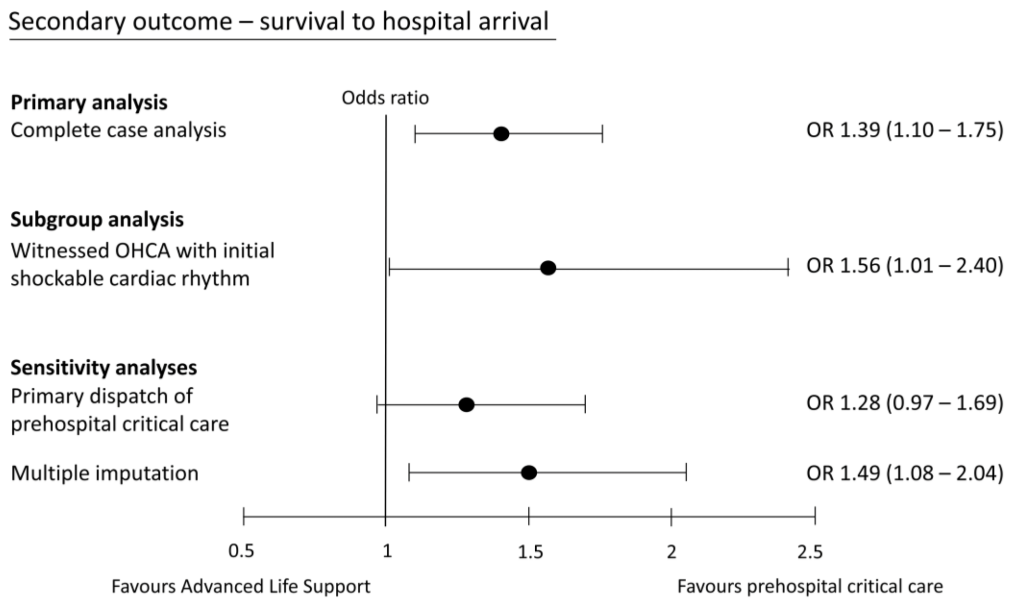
The sections above give details of a combination of a priori defined primary and secondary analyses of the primary and secondary outcomes as well as the post-hoc secondary analysis of a multiple imputation dataset. Figures 7.7 and 7.8 provide an overview of all key results from this section.

Figure 7.7 Odds ratios (95% confidence intervals) for prehospital critical care following out-of-hospital cardiac arrest, compared to Advanced Life Support; primary outcome



OHCA: Out-of-hospital cardiac arrest

Figure 7.8 Odds ratios (95% confidence intervals) for prehospital critical care following out-of-hospital cardiac arrest, compared to Advanced Life Support; secondary outcome



OHCA: Out-of-hospital cardiac arrest

7.3.9 Cost-effectiveness of prehospital critical care for out-of-hospital cardiac arrest

As discussed in the previous chapter, I entered the results of the primary analysis into the economic decision analysis model to calculate the incremental cost-effectiveness ratio (ICER) of prehospital critical care. Table 7.12 summarises the parameters of the model which were updated for this analysis.

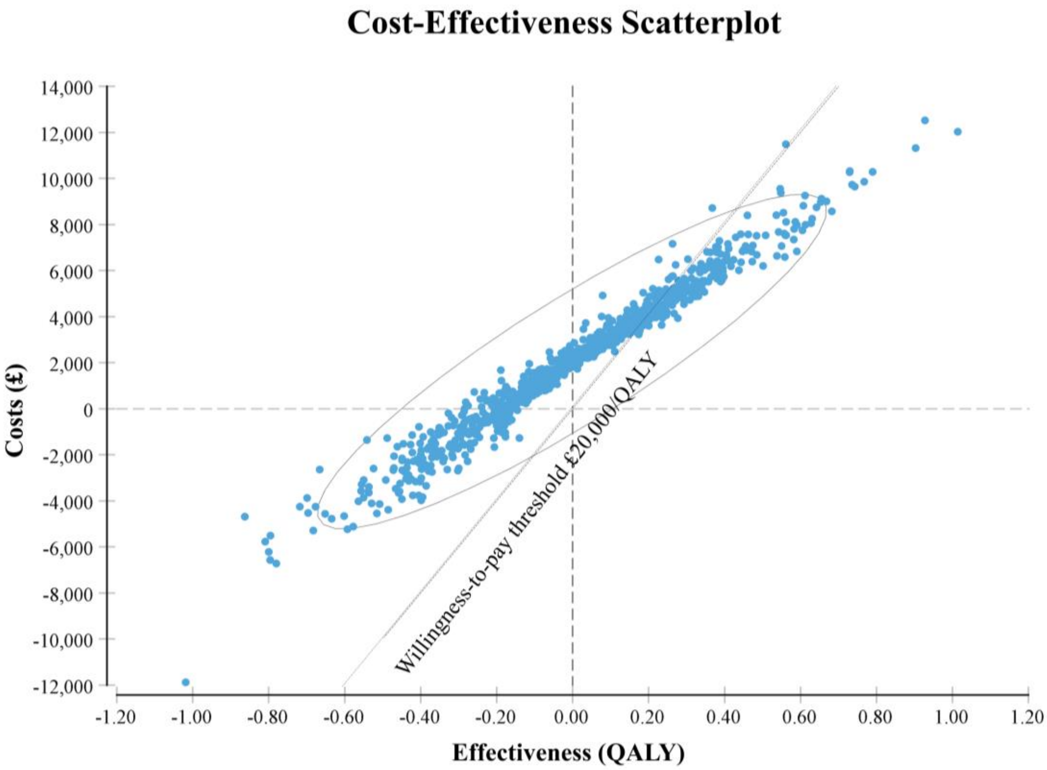
Table 7.12 Parameters of the cost-effectiveness analysis, updated from Table 6.4 (Chapter 6)

Parameters	**Cohort/ patient group**	**Mean value (95% CI)**	**Distribution**
Prehospital (decision tree model)			
p survival to hospital arrival	ALS	27.7% (25.7% - 29.8%)	Beta
	Critical care	34.4% (30.8% - 38.1%)	
In-hospital (decision tree model)			
p survival to hospital discharge	ALS	11.9% (10.5% - 13.5%)	Beta
	Critical care	11.9% (9.6% - 14.6%)	

CI: Confidence interval, p: probability, ALS: Advanced life support

The scatterplot in Figure 7.9 is a graphic representation of the results of the probabilistic sensitivity analysis of the complete model, showing 1,000 estimates for the ICER of prehospital critical care for OHCA. Of the 1,000 iterations, 189 are situated to the right of the willingness-to-pay (WTP) threshold of £20,000 per QALY. This means the probability of prehospital critical care for OHCA to be cost-effective, when compared to ALS prehospital care, is 18.9% (and the probability of not being cost-effective is 81.1%). Table 7.13 describes these probabilities further, by quadrants of the scatterplot in Figure 7.9.

Figure 7.9 Scatterplot of the incremental cost-effectiveness of prehospital critical care for out-of-hospital cardiac arrest, compared to Advanced Life Support



Each of the blue dots represents the result of one of the 1,000 iterations of the probabilistic sensitivity analysis. Dots situated to the right of the willingness-to-pay threshold indicate results of iterations which would be cost-effective at less than £20,000 per QALY. The ellipse indicates the 95% confidence interval.

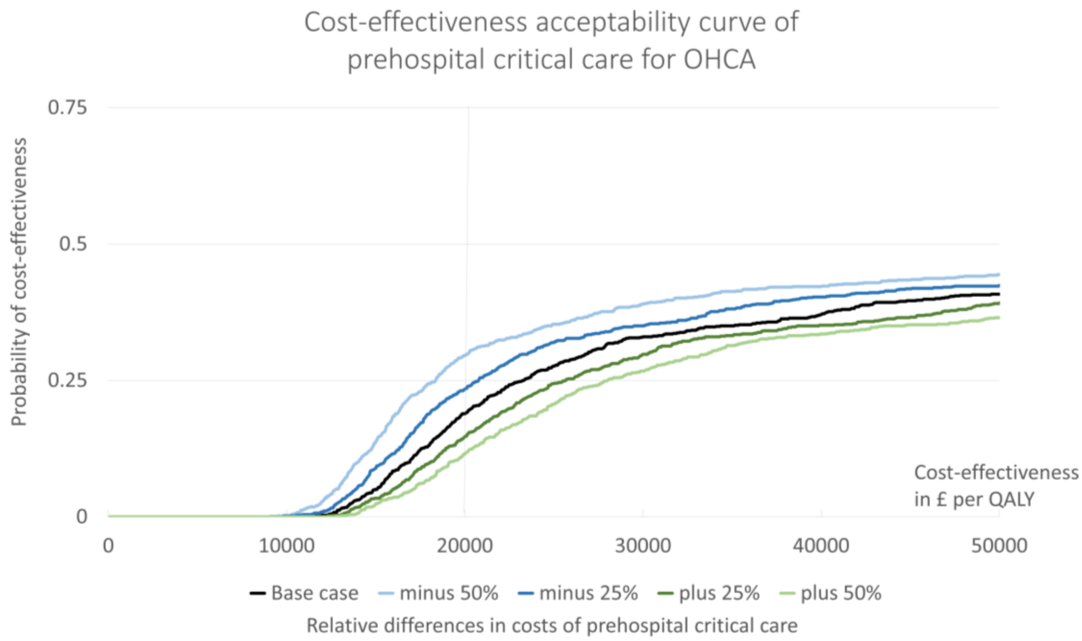
Table 7.13 Probabilities of incremental cost-effectiveness of prehospital critical care for out-of-hospital cardiac arrest by quadrant of the scatterplot in Figure 7.9

Quadrant	Cost of prehospital critical care*	Effect of prehospital critical care*	ICER	Probability**
Right upper quadrant	Higher cost	More effective	>£20,000	**30.1%**
	Higher cost	More effective	<£20,000	**18.9%**
Right lower quadrant	Lower cost	More effective	(superior)	**0%**
Left lower quadrant	Lower cost	Less effective	<£20,000	**0%**
	Lower cost	Less effective	>£20,000	**22.8%**
Left upper quadrant	Higher cost	Less effective	(dominated)	**28.2%**

**Compared to Advanced Life Support for out-of-hospital cardiac arrest. The grey shaded areas represent all scenarios considered cost-effective at a willingness to pay threshold of £20,000 per quality-adjusted life year. Red area represents least beneficial scenario of higher costs but less effectiveness.*
*** Probabilities are calculated from the proportion of iterations which fall into the corresponding area of the scatterplot.*
ICER: Incremental cost-effectiveness ratio

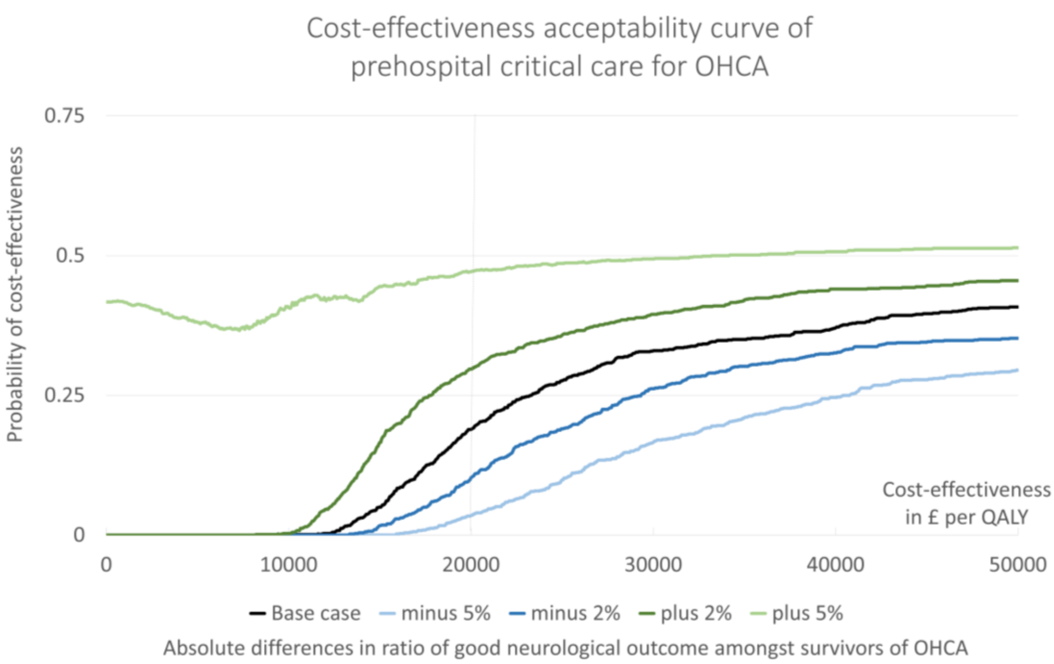
Due to the potential for prehospital critical care being delivered in configurations other than the helicopter-based service used for the cost analysis for this economic model, I undertook a sensitivity analysis, varying the costs of prehospital critical care by up to +/- 50%. Similarly, the proportion of good neurological outcome (Cerebral Performance Category (CPC) 1 or 2) amongst survivors of OHCA could have a potentially important impact on cost-effectiveness. In a second sensitivity analysis, I varied the proportion of survivors with CPC1-2 by up to +/- 5%. The results are presented in the form of cost-effectiveness acceptability curves in Figure 7.10 and Figure 7.11.

Figure 7.10 Cost-effectiveness acceptability curve of prehospital critical care for out-of-hospital cardiac arrest; includes a sensitivity analysis of varying costs of prehospital critical care



OHCA: Out-of-hospital cardiac arrest

Figure 7.11 Cost-effectiveness acceptability curve of prehospital critical care for out-of-hospital cardiac arrest; includes a sensitivity analysis of varying probabilities of good neurological outcome amongst survivors



OHCA: Out-of-hospital cardiac arrest

7.4 Discussion

Prehospital critical care teams attend patients with OHCA who have, on average, a higher chance of survival when compared to the patient cohort receiving ALS. Not surprisingly, therefore, the unadjusted rates were better in the prehospital critical care group. Once this imbalance was adjusted for, using propensity score analysis, the attendance of prehospital critical care teams at OHCA was associated with higher rates of survival to hospital arrival (secondary outcome), but not survival to hospital discharge (primary outcome). These results remained stable across a number of subgroup and sensitivity analyses. In this section, I will review these results in the context of previous research and the issues identified in the systematic review presented in Chapter 4.

7.4.1 A matter of sample size?

In Chapter 4, I described how three of the six observational studies which compared prehospital critical care for OHCA to ALS showed no difference in outcome, but were underpowered. The sample sizes for these studies were 1,029, 1,128 and 1,865, respectively (von Vopelius-Feldt, Coulter and Benger, 2015; Olasveengen *et al.*, 2009; Mitchell *et al.*, 1997). By comparison, the sample size of the primary analysis of this research is 2,505 and that of the multiple imputation analysis is 3,211. While this is an increase in sample size of approximately 30% to 50% compared to the studies showing no benefit, it is still considerably smaller than the sample sizes of two of the publications which do show benefit from prehospital critical care. Yasunaga *et al.* (2010) used a national database in Japan, which allowed them to analyse 95,072 cases of OHCA. Of note, only 3.7% of these patients received prehospital critical care. Hamilton *et al.* (2016) used propensity score analysis and compared outcomes between prehospital critical care and ALS for OHCA in groups of 7,854 cases each.

So is the lack of a significant effect of prehospital critical care on survival to hospital discharge after OHCA in this study simply a result of an underpowered sample size? Does the study need to be repeated with a larger sample? The current analyses have the power to detect an approximately 4-5% absolute difference in survival with an alpha of 0.8, but would a smaller benefit not also be important?

The answer to this question lies in the concept of the minimally important difference in outcome (Nichol *et al.*, 2016). In the context of OHCA, this has been primarily defined in terms of a minimally clinically important difference (MCID), and respondents in a survey indicated an absolute difference in survival of 4% (median, IQR 2-10) for the MCID in OHCA (Nichol *et* *al.*, 2016). However, the minimally important difference in outcome can also be defined in relation to the minimally economically important difference (Delgado *et al.*, 2013). In Chapter 6, I estimated the minimally economically important difference in survival, which prehospital critical care would need to achieve as 4%. While it is possible that a smaller benefit from prehospital critical care exists, for example in the range of a 1% to 2% absolute benefit in survival to hospital discharge, it is very unlikely that such a small benefit would be cost-effective, based on the results of the economic analysis presented in the previous chapter.

7.4.2 Which outcome measure best reflects the effect of prehospital critical care?

In Chapter 1, I discussed a number of ways in which the success of resuscitation efforts for OHCA can be measured. These include:

- Achieving ROSC at any time during the resuscitation
- Maintaining ROSC until the patient arrives at hospital (survival to hospital arrival)
- Survival to hospital discharge
- Neurological function either at discharge from hospital or within a given time-frame, usually 3-6 months

In general, the earlier outcomes are easier to measure and more specific to prehospital interventions, while the later outcomes are more patient-specific but require additional resources to be measured. For this thesis, I selected the most commonly reported outcome of survival to hospital discharge as the primary outcome – it is patient-focused but did not require any additional resources beyond the existing ambulance trusts' data collection systems. Somewhat disappointingly, the results convincingly show no association between prehospital critical care and improved survival to hospital discharge.

However, I also defined a secondary outcome a priori; survival to hospital arrival. In contrast to the primary outcome, analyses show a fairly consistent association between prehospital critical care and higher rates of survival to hospital arrival (Figure 7.7 and Figure 7.8), with an estimated absolute reduction of the risk of death prior to hospital arrival of 6.7%. The possible clinical explanation for these findings is that prehospital critical care teams manage to achieve and/or maintain ROSC in a higher proportion of patients. Unfortunately, most of these patients then die during their hospital stay, possibly due to the severity of the event leading to the OHCA or the physiological insult caused by the OHCA itself (see Chapter 1) (McCoyd and McKiernan, 2014; Reynolds and Lawner, 2012).

It is possible that, with improving post-OHCA care in hospital, the apparent effect of prehospital critical care on survival to hospital arrival might also translate into an increased survival to hospital discharge in the future. At the moment, however, the question remains of which of the two outcomes is more important. A patient surviving to hospital to then die within a few hours or days can be seen as an unnecessary prolongation of the dying process, and in Chapter 6 I analysed the healthcare costs associated with this. On the other hand, the qualitative research presented in Chapter 5 would indicate that there might be value for the relatives in the additional time allowed to process the dramatic event and to be at the patient's side and in the knowledge that modern medicine has been used to its full extent.

One outcome, which this research did not address, is the quality of life or neurological recovery of survivors of OHCA. While increasing the number of survivors following OHCA is an important goal, achieving a good functional outcome for as many survivors as possible is equally important (Soar *et al.*, 2015). This research did not try to assess if, amongst the survivors of OHCA, functional outcomes are affected by the provision of prehospital critical care. Due to the overall low number of survivors, a study addressing this question would require a much larger sample size and also considerable resources and complex consent procedures to obtain the necessary outcome measures.

Of the publications in the systematic review in Chapter 4, two included rates of good neurological function (CPC1 and CPC1-2) as outcome (see Table 4.2). For both studies, the information below is based on the unadjusted survival rates, as the information required was only provided in the unadjusted format. Olasveengen *et al.* (2009) provide rates of survival to hospital discharge and rates of discharge from hospital with CPC1-2. Survival to hospital discharge occurred in 10% and 13% (78 and 31) patients in the ALS and prehospital critical care groups, respectively. Good neurological function (CPC1-2) at discharge was measured in 75 (96%) and 29 (94%) of the patients in the respective groups. Similarly, in the study by Yasunaga *et al.* (2010), rates of survival at 1 month were 7.9% and 13.4% for the ALS and prehospital critical care groups, respectively. Of the 7,250 survivors in the ALS group, 36% had CPC1, and of the 287 survivors in the prehospital critical care group, 35% had CPC1. While it is certainly possible that prehospital critical care in this thesis has an unmeasured benefit in terms of improving functional outcomes amongst survivors of OHCA, such an effect has not been demonstrated in the limited previous research available.

7.4.3 Effects of dispatch decisions

The methods by which prehospital critical care providers are dispatched to OHCA is a major consideration when analysing and interpreting research in this area. The initial decision of whether to dispatch a prehospital critical care resource will be based on the often very limited information available from bystanders or first responders. In UK ambulance trusts, this information will be collected using the Medical Dispatch Priority System or NHS Pathways (NHS Digital, 2018b; Hardeland *et al.*, 2014). Both systems follow a simple algorithm of standardised questions. The information available for the initial decision to dispatch a prehospital critical care resource is therefore limited to a number of the Utstein variables, such as the patient's age, location of OHCA, witnessed event and bystander CPR (Hardeland *et al.*, 2014).

In five of the publications described in the systematic review in Chapter 4 and in the data presented in this chapter, prehospital critical care providers were more frequently dispatched to patients for whom these Utstein variables indicated a more positive prognosis. The result of this targeted dispatch is the overt bias discussed in the previous section, which has been adjusted for in this research as well as the publications of the systematic review. However, not infrequently the primary decision to dispatch or not dispatch a critical care resource is reversed, once additional information becomes available (Johnson and Sporer, 2010). This additional information may include cardiac rhythm, length of time without bystander CPR, length of the ongoing resuscitation, co-morbidities or premorbid quality of life of the patient. Similar to the information available during the initial dispatch decision, these factors are likely to be associated with the likelihood of patient survival. However, only few are recorded as part of the Utstein criteria, leading to potential hidden bias.

Of the publications included in the systematic review, only Hiltunen *et al.* (2016) discuss this issue and consider it to be a potential factor underlying the association between prehospital physicians attending OHCA and survival in their study. This thesis is the first attempt to formally examine the impact of the complexity of prehospital critical care dispatch. The first thing to note is that reversal of the initial dispatch decision occurs frequently. 70 out of 534 (13%) primary decisions to dispatch prehospital critical care providers to an OHCA were reversed. On the other hand, in 191 of 655 (29%) cases where prehospital critical care teams attended a patient with OHCA, they were only dispatched once requested by ALS ambulance crews on scene. Table 7.10 gives an overview of the different survival rates for each of these scenarios.

In the sensitivity analysis which excluded all cases where primary dispatch decisions were reversed, the overall effect is towards less effectiveness of the prehospital critical care team;

see Figure 7.7 and Figure 7.8. These findings support the hypothesis that the current method of dispatch of prehospital critical care biases apparent success rates of critical care resuscitations for OHCA, which might be an explanation for the strong views held by some stakeholders about the effectiveness of prehospital critical care in the treatment of patients with OHCA (Chapter 5).

7.4.4 Comparison of findings to previous research

The results presented in this chapter are in contrast to those of arguably the two most important previous publication on the topic of prehospital critical care for OHCA. Both Yasunaga *et al.* (2010) and Hamilton *et al.* (2016) show an association between prehospital critical care provided by physicians and improved survival rates, when compared to ALS care by paramedics. In this section, I will use the PICOS system to describe how differences in each of these five domains may account for this difference in results.

7.4.4.1 Population

Yasunaga *et al.* (2010) studied only a subgroup of OHCA patients, those with witnessed OHCA. This population would have a higher chance of survival, compared to also including patients with unwitnessed OHCA (Hawkes *et al.*, 2017). Any treatment effect might therefore be more pronounced in this population of patients. Hamilton *et al.* (2016, p.96) do not explicitly state the inclusion criteria for their study, but mention that the "*study population included persons registered with OHCA of any cause"*. As the less common causes of traumatic or paediatric OHCA result from different pathophysiological processes and require different interventions, I considered them to be a patient group which should be studied independently from the much more commonly occurring adult, non-traumatic OHCAs included in my research. Hamilton *et al.* (2016) do not provide information on the aetiology of OHCAs included in their research, but it is possible that the documented effect of prehospital critical care is due to an effect in patient groups which were not included in this thesis.

7.4.4.2 Intervention

It is likely that the configuration of prehospital critical care differed between my research and the two studies undertaken in Denmark and Japan. One major difference is the focus of this research on prehospital critical care. Both Hamilton *et al.* (2016) and Yasunaga *et al.* (2010) primarily investigated the effect of prehospital physicians. As the next chapter will provide a detailed description of the prehospital critical care delivered in this research, I will defer further comparison of the configurations of prehospital critical care, and their potential impact on outcomes, to the next chapter.

7.4.4.3 Comparator

When examining the effects of prehospital critical care on survival following OHCA, the comparator in my research and the other studies, is prehospital ALS. While ALS protocols vary only minimally internationally, there is considerable variation in the training and competencies of ALS providers, between different EMS systems and also over time. Hamilton *et al.* (2016) analysed OHCAs occurring in Denmark between 2005 and 2012, while my study period is more recent; 2016 to 2017. Figure 7.12, taken from Hamilton *et al.* (2016), shows unadjusted rates of survival during the study period (note that patients in the physician group had better prognostic factors).

Figure 7.12 Hamilton *et al.* (2016): unadjusted primary outcome of 30-day survival following out-of-hospital cardiac arrest during the study period from 2005 to 2012, with permission from Resuscitation (license number 4341331380285)

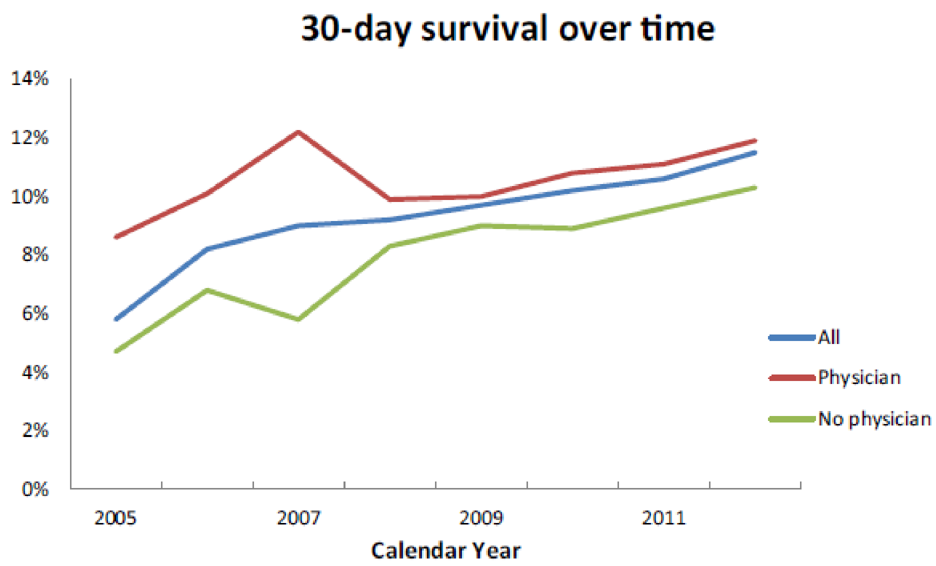


Figure 7.12 demonstrates an overall gradual improvement in survival but also a much wider gap between survival rates for physician (prehospital critical) care around 2007, followed by a more narrow difference after 2008. In an exploratory stratified analysis, Hamilton *et al.* (2016) demonstrate a significant benefit from prehospital critical care for OHCA for the years 2005-2008, but not for the years 2009-2012 (OR 1.39, 95%CI 1.08 – 1.79 and OR 1.11, 95%CI 0.96 – 1.29, respectively). A possible explanation for the lack of benefit from prehospital

critical care is therefore an improvement in prehospital ALS for OHCA. Of note, the Danish EMS system underwent a major reconfiguration with increased training and updated equipment for prehospital providers around 2009 (Frischknecht Christensen *et al.*, 2016). The unadjusted survival rates in the ALS cohort are very similar to those observed in my research, and it is likely that modern UK ALS-paramedic practice is more similar to the later study period of Hamilton *et al.* (2016).

Similarly, ALS care in the study by Yasunaga *et al.* (2010) is likely to be quite different from modern UK ambulance service practice. While a detailed description of the Japanese ALS prehospital system is beyond the scope of this thesis, the study's description of the ALS providers during the study period of 2005 to 2007 indicates that the training, autonomy and clinical competencies of the Japanese ALS providers was considerably less than that of modern ALS paramedics in the UK (Brown *et al.*, 2016; Yasunaga *et al.*, 2010).

In summary, there is a strong possibility that the lack of effect of prehospital critical care on survival following OHCA in this study is not due to less effective prehospital critical care, but more effective ALS, when compared to the other two studies.

7.4.4.4 Outcomes

A further difference between my research and the two studies showing benefit from prehospital critical care is the choice of primary outcome. I chose the pragmatic, albeit slightly less patient oriented, outcome of survival to discharge, while Hamilton *et al.* (2016) and Yasunaga *et al.* (2010) used 1-month survival and good neurological function at 1 month. As discussed in Section 7.4.2 and also evidenced in Chapter 6, these outcomes are closely correlated, and this difference in primary outcome is unlikely to contribute to the difference in findings.

7.4.4.5 Study design

The studies by Yasunaga *et al.* (2010) and Hamilton *et al.* (2016) are both retrospective observational analyses of national OHCA databases. In contrast, data collection in my research was prospective, which (within limits) allowed me to address additional potential confounders not included in the other studies. This includes the mechanisms of dispatch of prehospital critical care teams (Sections 7.2.11 and 7.3.7) and the potential effects of cardiac centres (to be addressed in the next chapter).

Both Yasunaga *et al.* (2010) and Hamilton *et al.* (2016) used adjustment methods to account for the imbalance of prognostic factors. Yasunaga *et al.* (2010) used MLR, rather than propensity score analysis which means there is a higher possibility of unmeasured confounding, favouring prehospital critical care (Holmes, 2014). In addition, the MLR model used by Yasunaga *et al.* (2010) did not include the Utstein location of OHCA, which is both associated with prehospital critical care attendance and survival rates in other research (Granfeldt *et al.*, 2017; von Vopelius-Feldt, Coulter and Benger, 2015).

Hamilton *et al.* (2016) used 1:1 propensity score matching as their primary analysis and showed a statistically significant benefit from prehospital critical care teams (OR 1.18, 95%CI 1.04 – 1.34). Two secondary analyses, using MLR on complete cases and a multiple imputation dataset, failed to show any benefit (OR 1.06, 95%CI 0.91 – 1.24 and OR 1.07, 95%CI 0.92 – 1.24). The lack of significant effect with MLR analysis but a significant effect with propensity score analysis is somewhat contrary to what one would expect when comparing the two methods (Shah *et al.*, 2005).

One possible explanation is the matching procedure used in the propensity score analysis by Hamilton *et al.* (2016). While details are limited in the published manuscript, it seems likely that matching on the propensity score was done with replacement of matched cases. In my research, each OHCA patient with ALS care was used only once in the matching process. In contrast, matching with replacement returns each matched OHCA case back into the pool of possible matches for the next pair (Guo and Fraser, 2010). While this matching process makes balance of covariates easier to achieve, the downside is that individual cases can be matched multiple times. These multiple-matched cases can have a disproportionate impact on the measured outcomes and bias the results in an unpredictable fashion (Stuart, 2010).

Evidence of multiple matching of subgroups of patients exists in the study by Hamilton *et al.* (2016). For example, of 7931 patients in the ALS group, only 1,173 had an OHCA in an urban area. However, in the propensity score-matched cohort, this absolute number nearly doubled to 2,235 (Hamilton *et al.*, 2016). When matching with replacement, in theory, an individual patient could be matched hundreds of times and it is therefore recommended to monitor for the frequency of matches for each case. Unfortunately, this information is not provided by Hamilton *et al.* (2016), making it difficult to assess if the matching method resulted in biased estimates of treatment effects.

7.4.5 Cost-effectiveness of prehospital critical care

The decision analysis model constructed in Chapter 6 showed that, amongst other factors, the cost-effectiveness of prehospital critical care depends on the secondary and primary outcome of the research presented in this chapter: survival to hospital arrival and survival to hospital discharge, respectively. Higher rates of survival to hospital arrival increase the costs associated with prehospital critical care, without increasing its effectiveness. On the other hand, higher rates of survival to hospital discharge increase the effectiveness and, to a lesser degree, costs. Given the higher rates of survival to hospital arrival without increased survival to hospital discharge observed in this research, it is not surprising that the economic analysis undertaken on the now completed model shows prehospital critical care to be extremely unlikely to be cost-efficient.

One might consider the probability of cost-effectiveness of 18.9% at a WTP threshold of £20,000 per QALY encouraging. However, I would caution the reader against interpreting this probability with undue optimism. It very likely represents the uncertainty of the data that underlies the model, with most probabilities and costs being sampled from distributions (see Chapter 6, Table 6.4), rather than being used as single value in the model. At the other end of the spectrum introduced by the probabilistic sensitivity analysis is the possibility that prehospital critical care is not only more expensive than ALS for OHCA, but also less effective. The probability for this scenario (28.2%, Table 7.13) is considerably higher than the probability of cost-effectiveness.

Of note, the actual costs of prehospital critical care do not change the likelihood of cost-effectiveness substantially, even when decreased by 50% (Figure 7.10). Varying the proportion of survivors with good neurological outcome had a bigger effect on possible cost-effectiveness, likely due to the significant long-term care costs associated with poor neurological survival. However, as outlined in Section 7.4.2, there is no evidence in the limited current literature to suggest that prehospital critical care has an effect on this ratio.

Likewise, the probability of cost-effectiveness does not change significantly if higher willingness-to-pay thresholds are considered. The cost-effectiveness acceptability curves in Figure 7.10 and Figure 7.11 remain at probabilities of less than 50% for cost-effectiveness of prehospital critical care for OHCA, even at WTP thresholds of £30,000 or £40,000 per QALY.

7.5 Challenges and limitations

The challenges and limitations of this chapter can be divided into those pertinent to the amount and quality of data used, and the data analysis process which aimed to eliminate bias and assert causation. I will address these aspects in the following paragraphs.

7.5.1 Data quantity - delays in data transfers

As described in Section 7.3.1, the research project experienced considerable delay of data transfer from two of the four participating ambulance trusts. I was unable to exert any influence on the process of data transfer from the ambulance trusts to the OHCAO Registry, as this process had already been established and continued independently of my research. While the OHCAO staff warned me at the very beginning that data would take a considerable amount of time to reach me via this data stream, the expectation initially was one of delays of 6 to 9 months. The resulting reduction in available data was partially compensated for by a larger than expected number of OHCAs per participating ambulance trust, with and without prehospital critical care attendance. The sample size in this analysis was therefore close to the estimation in Section 7.2.9, which corresponds to a power of 0.8 to detect an absolute difference in survival of 4%. This is in keeping with what stakeholders consider a minimal clinically important difference in survival to hospital discharge after OHCA (Nichol *et al.*, 2016) and also my own estimation of a minimally economically important difference, calculated in the economic analysis in Chapter 6.

7.5.2 Data quality – identification of out-of-hospital cardiac arrest

The first challenge was to assure that all prehospital critical care involvement in OHCA care was recorded accurately. For all but one critical care service, this was done through existing electronic databases. All activities of the critical care services are recorded on these databases and form part of their medico-legal documentation, governance and/or activity report processes. As such, they can be assumed to be highly accurate. For the one critical care service which required paper-based recording of involvement in OHCA, I was concerned that providers might be less likely to complete the required form for OHCAs with poor outcome, leading to inaccurate labelling of these cases as ALS care only. To mitigate this potential effect, a member of the critical care service's clinical team volunteered to check completed forms against the service's activity log and to assure completion of forms for all OHCA cases recorded on the (reliable) electronic activity log.

The second data stream, containing the Utstein variables and outcome data from all OHCAs, was provided from the OHCAO Registry. In all ambulance services, this relies on a prehospital provider to complete a paper or electronic OHCA form, which is then identified by the ambulance trusts' research and audit teams. To my knowledge, none of the ambulance trusts had the capacity to check the completion rate of these forms for OHCAs, and it is therefore likely that not all cases of OHCA are recorded on the OHCAO database. While this has an obvious negative effect on the sample size and power of this analysis, a potential bigger problem is if cases are missing in a systematic fashion and if the reason for this is associated with the intervention and/or outcome studied. Having personally experienced the data collection process from the prehospital provider perspective, I am fairly confident that cases are likely missing at random (i.e. due to errors in documenting case numbers) and independently of prehospital critical care attendance or survival. However, I am unable to investigate or prove this formally within the limitations of this research.

7.5.3 Data quality – missing variables

Table 7.6 gives an overview of the relative amount of missing variables in the OHCAO dataset used. For my primary analysis, I used a complete case analysis strategy defined a priori, excluding any cases with missing variables. While most variables only had a negligible rate of missing values, cardiac rhythm and survival to hospital discharge were missing more frequently. These missing data are of particular concern as cardiac rhythm is the most powerful predictor of the primary outcome, survival to hospital discharge (Wibrandt *et al.*, 2015).

The optimal strategy of dealing with missing variables is the subject of ongoing debate (Pedersen *et al.*, 2017; Galati and Seaton, 2016; Groenwold *et al.*, 2012). Exclusion of cases with missing data is considered appropriate where data are missing completely at random, while multiple imputation is the method of choice if data are missing at random but conditional on the observed data (Hayati Rezvan, Lee and Simpson, 2015). Figure 7.6 demonstrates that neither rhythm nor survival to hospital discharge are missing at random in this dataset, but that the frequency of missing values depend on other observed variables.

To mitigate the potential confounding caused by this, I undertook a sensitivity analysis of the dataset, using multiple imputation for missing values of cardiac rhythm and survival to hospital discharge; see Section 7.3.7. The resulting odds ratios for the effect of prehospital critical care on survival following OHCA are consistent with the primary analysis presented in this chapter, as is the other sensitivity and the subgroup analysis.

7.5.4 Data analysis – overt bias

Ideally, the propensity score matching process would result in a balance of covariates across the groups of prehospital critical care and ALS care for OHCA. In this case, the effect of prehospital critical care on survival could simply be estimated by comparing survival rates between the two groups. However, there is no clear definition of what constitutes an adequate balance of covariates. The use of significance tests and display of p-values is frequently seen in practice (Hamilton *et al.*, 2016) but discouraged as potentially misleading (Holmes, 2014). Austin (2009) recommends the use of a combination of standardised differences, visual examination of graphs and common sense. Following this recommendation, I used a combination of standardised differences (Table 7.8) and a subjective assessment of: does this covariate seem well enough balanced for me to consider them clinically equal? Unfortunately, despite the iterative steps of propensity score matching described in Section 7.2.7, a number of covariates were still not equally distributed between the prehospital critical care and ALS group. Of note, the remaining imbalances would generally have favoured survival in the prehospital critical care group.

7.5.5 Data analysis – hidden bias

The challenge posed by overt bias is largely that of adequate methods of adjustment (Lu, 2009). However, it is not only overt bias which can result in erroneous estimates of treatment effects in observational research, but the more difficult to control hidden bias (Holmes, 2014). This stems from variables which are associated with the intervention and the outcome, but not measured.

For example, in contrast to my research, Hamilton *et al.* (2016) were able to include patients' co-morbidities and rural versus urban location in their analysis. Critical care teams in the study by Hamilton *et al.* (2016) attended patients with less co-morbidities and more frequently in urban settings. While neither factor has been clearly shown to influence survival following OHCA (Beesems *et al.*, 2015; van de Glind *et al.*, 2013; Jennings *et al.*, 2006), this might be due to the limitations of existing research, rather than an actual lack of effect.

Further potential unmeasured confounders include the length of time between the OHCA occurring and being recognised in unwitnessed events or the quality of bystander CPR. Importantly, all the potential confounders listed here would be associated with at least one measured confounder. For example, the unmeasured confounder of co-morbidity has a strong correlation with the measured confounder of age (Prince *et al.*, 2015). As such, propensity score matching in this thesis would have at least partially adjusted for differences in co-morbidities between the groups. By balancing age, co-morbidities, through their association with age, would have also been partially balanced (Guo and Fraser, 2010). Of course, the problem is that it is impossible to measure how well this feature of propensity score analysis worked, due to the very nature of the unmeasured confounders.

Of note, any unmeasured confounding would have likely influenced the results in the direction of an apparent benefit from prehospital critical care for OHCA. Given that the results did not show an association between prehospital critical care and higher survival rates following OHCA, concerns about potential unmeasured confounding favouring prehospital critical care are less important than if the analysis had shown an association with higher survival rates. I will further discuss the issue of confounding in Chapter 9.

7.6 Conclusions

Prehospital critical care teams in this research attended patients with, on average, better prognostic factors for survival following OHCA, compared to ALS paramedics. Once this imbalance is adjusted for, using propensity score matching, there is an association between prehospital critical care attendance and short-term survival to hospital arrival (secondary outcome), but not longer-term survival to hospital discharge (primary outcome). These results are stable over a number of subgroup and sensitivity analyses. The lack of proven clinical effectiveness in combination with higher costs associated with prehospital critical care result in a very low probability of prehospital critical care being cost-effective, even at higher willingness-to-pay thresholds or within a number of sensitivity analyses.

7.7 What next?

With the somewhat disappointing but also convincingly consistent results of this chapter, the obvious next step would be to return to the overall aim of this thesis; "*to provide key stakeholders in prehospital care with the information required to guide the funding and configuration of prehospital critical care for OHCA".* Do we need to improve prehospital care for OHCA? How much are we willing to spend? Is there a future for prehospital critical care for OHCA? I will attempt to answer these essential questions in Chapter 9.

Prior to this, a few important other questions need to be addressed. Firstly, the intervention of prehospital critical care has been established based on a number of theoretical benefits, described in detail in the Introduction chapter. Early optimised neuro-protective post-resuscitation care and transfer to a cardiac arrest centre by prehospital critical care teams are thought to be beneficial (Schober *et al.*, 2016), so why is there no benefit demonstrated in this research?

Secondly, this chapter only examined the overall effect of a number of prehospital critical care teams on survival following OHCA. Each service operates a different model, and it is possible that this translates into different clinical effectiveness for OHCA care. The detailed analysis of prehospital critical care interventions during the treatment of patients with OHCA presented in the next chapter will aid in understanding some of these questions.

8. Original research: an analysis of prehospital critical care interventions for out-of-hospital cardiac arrest

8.1 Introduction

In the previous chapter, I analysed the effects of prehospital critical care, as a concept, on survival following out-of-hospital cardiac arrest (OHCA). When compared to Advanced Life Support (ALS) delivered by paramedics, the analysis showed higher rates of short-term survival to hospital arrival, but no increased rates of survival to hospital discharge with prehospital critical care for OHCA. Data for this analysis were collected from six different prehospital critical care services in two ambulance trusts. Each critical care services operated their own unique system, shaped by the geography and population covered as well as their funding and previous historical developments (von Vopelius-Feldt and Benger, 2014a; Jashapar, 2011). An important consideration, therefore, is the degree to which differences in the delivery of prehospital critical care in this research might have influenced its effectiveness.

In Chapter 1, I provided an overview of potential prehospital critical care interventions which might improve outcomes, including the general lack of evidence for any given intervention (Jentzer *et al.*, 2016). The systematic review presented in Chapter 4 highlighted the issue of prehospital critical care being only poorly or not at all described in the literature examining its effects. This results in difficulties in the interpretation and generalisation of the research findings. In addition, two of the five stakeholder groups involved in the research presented in Chapter 5 expressed an interest in a deeper understanding of the mechanisms of prehospital critical care for OHCA. The patient and public involvement (PPI) group thought that this information was an important aspect of weighing up the ethical issues of randomising prehospital critical care and understanding how it differs from the current standard of ALS. Ambulance service commissioners were also keen on understanding the interventions delivered by prehospital critical care providers, to identify the most cost-effective mode of delivery.

Due to the limitations of the observational research design which are further discussed in the next section, this chapter will stop short of an attempt to link individual prehospital critical care interventions to survival following OHCA. Instead, I will take a more descriptive approach, addressing the following questions:

- Are there important differences in the configuration or effectiveness of the individual prehospital critical care services?
- What are the potential reasons for a lack of survival benefit associated with prehospital critical care?
- What critical care interventions are being undertaken and how frequently?

8.2 Methods

8.2.1 Developing the protocol

The original objective stated in the research proposal at the beginning of this thesis was *"to examine which prehospital critical care interventions contribute to improved survival from OHCA"*. This aim of demonstrating causality was already slightly adjusted in the protocol published during the first year of my PhD, which lists "*the association between individual critical care interventions and survival"* amongst the aims (von Vopelius-Feldt *et al.*, 2016, p.47). At the time of writing this chapter, in the third and final year of my PhD, I have further revised the aim of this chapter from causation to association to description of prehospital critical care interventions. The reasons for this gradual shift towards the current and final aim of this chapter were largely caused by a better understanding of confounding and bias in observational research, the limitations of multiple logistic regression (MLR) as a tool to adjust for these factors and an interim review of data received from participating prehospital critical care services.

In contrast to ALS, the use of prehospital critical care interventions for patients with OHCA does not follow a uniform treatment algorithm (Soar *et al.*, 2015; von Vopelius-Feldt and Benger, 2014b). Instead, the decision to undertake or omit given interventions are often based on a combination of individual patient factors and the provider's perception of the likelihood of benefit to the patient and overall chances of a successful resuscitation. For example, intravenous Sodium Bicarbonate during OHCA is often given as a last therapeutic attempt after a prolonged resuscitation and, in observational research, is therefore associated with poor survival rates following OHCA (Kawano *et al.*, 2017). This effect is reduced when confounding factors are adjusted for, but whether it is truly harmful or even beneficial in the care of OHCA continues to be debated in the absence of randomised controlled trials (Celik *et al.*, 2016).

Statistical methods, such as propensity score analysis (see Chapter 6) can adjust for many of these confounders, but only if they have been recorded. During OHCA, the confounders will largely consist of the frequently recorded Utstein variables (see Chapters 1 and 6). However, after return of spontaneous circulation (ROSC) other factors, such as the patient's neurological and haemodynamic state or comorbidities will be more important, none of which were recorded in the dataset available for this research. The concern about unmeasured confounding and hidden bias is therefore a major reason to avoid attempts to show associations or causation between individual prehospital critical care interventions and outcomes.

The method of adjustment which I envisaged using at the start of the PhD was MLR. It would allow me to control for the measured confounding factors while examining the associations between the large number of potential critical care interventions and survival to hospital discharge. However, this approach would have risked finding significant associations between interventions and outcome by pure chance, as further discussed in Section 8.5.1.

An alternative would have been to undertake a separate propensity score analysis for each individual intervention. It was clear that this approach would not only be time consuming but also very likely impossible, once I reviewed an early sample of data submitted from the prehospital critical care services. Many interventions were only delivered a handful of times. In combination with the overall low survival rates, the anticipated sample size of OHCA patients in the prehospital critical care group of 600 to 1,500 was simply not enough to make any meaningful statements about statistically significant associations (Hsieh, Bloch and Larsen, 1998). Instead, I opted for a largely descriptive approach to data presentation and analysis, with selective use of propensity score analysis where appropriate and feasible.

8.2.2 Participating prehospital critical care services

Overall, six prehospital critical care services (PCCs) in two ambulance trusts contributed to data collection for the analysis of the effect of prehospital critical care on survival following OHCA, presented in Chapter 7. Of these, four services also provided details about interventions delivered by their critical care providers. See Table 8.1 for an overview of the prehospital critical care services and their key features. The remaining two prehospital services provided data on which cases of OHCA they attended but no details regarding the interventions delivered and therefore are excluded from this analysis.

Table 8.1 Overview of prehospital critical care services

Prehospital critical care service	Funding	Description	Ambulance trust
PCC-1	Mainly charity, some NHS	Physician and CCP team dispatched by helicopter or RRV, mixed urban to rural geography.	Trust Alpha
PCC-2	Mainly charity, some NHS	Two bases with helicopter and RRV each, rural geography. Mostly CCPs with physician involvement in some cases.	Trust Alpha
PCC-3*	Mainly charity, some NHS	Paramedic-staffed helicopter and RRV, with variable physician presence	Trust Alpha
PCC-4*	Charity	Single critical care physician, responding on RRV	Trust Alpha
PCC-5	Charity	Physician and paramedic team dispatched by RRV throughout the ambulance service.	Trust Beta
PCC-6	Mainly charity, some NHS	Physician and paramedic-staffed helicopter, not routinely dispatched to OHCA	Trust Beta

**No details about interventions available*
PCC: Prehospital critical care service, NHS: National Health Service, CCP: Critical care paramedic, RRV: Rapid response vehicle

8.2.3 Inclusion and exclusion criteria

These are the same as described in Chapter 7; in short, non-traumatic adult OHCA. In addition, patients had to be attended by one of the six prehospital critical care services listed in Table 8.1.

8.2.4 Data collection

The data collection process is described in detail in Chapter 7. Patient demographics, Utstein variables and outcomes were provided by the Out-of-Hospital Cardiac Arrest Outcome (OHCAO) Registry at the University of Warwick. Information on the dispatch of prehospital critical care providers and interventions delivered was obtained from the participating services; see also Table 7.3 in Chapter 7 and Tables 8.3 and 8.4 in the following section. All interventions delivered were entered prospectively by one of the prehospital critical care providers at the scene of the OHCA or shortly thereafter, with the process tailored to each service's existing documentation system; see Table 8.2.

Table 8.2 Data collection process for each prehospital critical care service which provided data on prehospital critical care interventions

Prehospital critical care service	Data collection process
PCC-1	Providers entered case details into an existing local electronic database, which was adjusted for the purpose of this research. I extracted data in monthly intervals during the study period.
PCC-2	Paper data collection forms were distributed at both bases; see Appendix D1. One CCP volunteered to lead the process locally, he checked completed forms against the local database and assured forms were completed for all OHCAs. Forms were scanned and sent to me via secure email. I transferred data into an Excel spreadsheet.
PCC-5 and PCC-6	Providers entered case details into existing electronic patient care forms used throughout the trust. A research paramedic identified all critical care cases on the trusts' electronic database, extracted the relevant information and sent to me in 6-month intervals.

PCC: Prehospital critical care service , CCP: Critical care paramedic, OHCA: Out-of-hospital cardiac arrest

8.2.5 Prehospital critical care interventions

The list of prehospital critical care interventions which might be delivered during OHCA was based on my own previous research into prehospital critical care competencies (von Vopelius-Feldt and Benger, 2014b). An initial list of interventions was reviewed and updated by the steering group. This list was then further adjusted for each participating prehospital critical care service, to reflect slight differences in their practice. For example, rapid sequence induction of anaesthesia (RSI) currently requires the presence of a physician and is therefore not undertaken in any of the systems operating without physicians. RSI was therefore taken off the list of requested interventions for those services, in order to create an bespoke and effective data collection process. Tables 8.3 and 8.4 show the complete list of all potential critical care interventions during OHCA and after ROSC, respectively.

Table 8.3 List of potential prehospital critical care interventions during out-of-hospital cardiac arrest

Intervention during OHCA	**Description of use in adult, non-traumatic OHCA**	**Reference**
Ultrasound use	Increasingly used during OHCA to detect reversible causes or confirm futility of resuscitation. Only low quality level evidence to support either indication.	Tsou *et al.* (2017)
Surgical airway	Potentially life-saving in the rare event of a *„can't intubate can't ventilate"* situation.	Collopy, Kivlehan and Snyder (2015)
Central venous access	Rarely used during OHCA due to the time required to complete the procedure. Might be useful for drug administration in prolonged resuscitation.	Leidel *et al.* (2012)
Mechanical chest compression	Shown not to improve survival after OHCA in randomised controlled trial. Might allow transfer during OHCA or free up providers for other tasks.	Perkins *et al.* (2015)
Atropine IV	Removed from ALS guidelines but still occasionally used on clinical grounds in bradycardic PEA arrest.	SOS-KANTO Study Group (2011)
Magnesium IV	Might improve conversion rates of VF to ROSC in refractory VF but no clear evidence of benefit.	Huang *et al.* (2013)
Calcium IV	Counter-acts the arrhythmogenic effects of hyperkalaemia as rare cause of OHCA. Unclear if this translates into benefits in OHCA.	Wang *et al.* (2016)
Sodium Bicarbonate IV	Thought to improve acidosis in prolonged resuscitation but might worsen intra-cellular acidosis and result in worse long-term outcomes.	Kawano *et al.* (2017)
Thrombolysis	Revascularisation of blocked coronary artery in OHCA due to AMI. No benefit in randomised controlled trial of adult OHCA.	Bottiger *et al.* (2008)
Thoracostomy	Relief of tension pneumothorax as a very rare reversible cause of OHCA.	Beun *et al.* (2015)
Peri-mortem hysterotomy	Potentially life-saving for mother and fetus in rare case of OHCA during the third trimester.	Soar *et al.* (2010)
Blood transfusion	Potentially life-saving in rare case of OHCA due to non-traumatic massive haemorrhage if findings from major trauma research can be extrapolated.	Huang and Dunham (2017)
ROLE outside of JRCALC guidelines	Decision to terminate resuscitation on clinical grounds, rather than algorithms might be more patient-focused and efficient.	Ranola *et al.* (2015)
Other interventions	Any non-ALS intervention not listed above	N/A

OHCA: Out-of-hospital cardiac arrest, IV: Intravenous, ALS: Advanced Life Support, PEA: Pulseless electrical activity, VF: Ventricular fibrillation, ROSC: Return of spontaneous circulation, AMI: Acute myocardial infarction, ROLE: Recognition of life extinct, JRCALC: Joint Royal Colleges Ambulance Liaison Committee

Table 8.4 List of potential prehospital critical care interventions after return of spontaneous circulation

Intervention after ROSC	Description of use in adult, non-traumatic OHCA	Reference
Rapid sequence induction of anaesthesia	Allows for airway protection, optimal ventilation and neuroprotection. Complex intervention without clear evidence of benefit.	von Vopelius-Feldt and Benger (2013)
Sedation and/or paralysis	Allows for optimal ventilation and neuroprotection in patients where an advanced airway was already placed during OHCA. Not studied in the prehospital phase of OHCA care.	Girotra, Chan and Bradley (2015)
Central venous access	Standard for in-hospital care, allows for reliable infusion of post resuscitation drugs. Rarely used during prehospital care for OHCA.	Leidel *et al.* (2012)
Inotropes or vasopressors IV	Maintain sufficient blood pressure to optimise organ perfusion. Potential benefits extrapolated from in-hospital treatment.	Trzeciak *et al.* (2009)
Amiodarone IV	Good evidence for the treatment and prevention of tachy-arrhythmias occurring in critically ill patients.	Trappe, Brandts and Weismueller (2003)
Magnesium IV	Frequently used as adjunct in the management of tachy-arrhythmias in critically ill patients, benefits have not consistently been shown.	Trappe, Brandts and Weismueller (2003)
Sodium Bicarbonate IV	Thought to improve acidosis after OHCA but might exacerbate intra-cellular acidosis and result in worse long-term outcomes.	Kawano *et al.* (2017)
Calcium IV	Treatment for hyperkalaemia, which might be the cause or consequence of an OHCA.	Mahoney *et al.* (2005)
Synchronised cardioversion	Treatment of tachy-arrhythmias causing haemodynamic instability, common after OHCA.	Roth *et al.* (2003)
Ultrasound	Used to guide haemodynamic resuscitation, frequently used during in-hospital treatment of critically ill patients.	Lichtenstein *et al.* (2014)
Blood transfusion	Reduces the negative effects of haemorrhagic shock as rare cause of non-traumatic OHCA.	Engelbrecht, Wood and Cole-Sinclair (2013)
Air transfer	Rapid transfer when the OHCA occurred a long distance from the destination hospital. No clear benefit in the UK setting.	Taylor *et al.* (2010)
Bypass of nearest hospital for cardiac centre	Current evidence strongly suggests that outcomes after OHCA are better for patients treated at high-volume cardiac centres with 24/7 PCI capability.	Schober *et al.* (2016)
Other interventions	Any non-ALS intervention not listed above	N/A

ROSC: Return of spontaneous circulation, OHCA: Out-of-hospital cardiac arrest, IV: Intravenous, UK: United Kingdom, PCI: Percutaneous coronary intervention

8.2.6 Data analysis

Data analysis was tailored to fit each of the three questions outlined, while considering the limitations of the available data to address each of the questions. When examining potential reasons why prehospital critical care was not associated with improved survival in the previous chapter, I focused on the potential factors listed below. The list is unlikely exhaustive, but includes the main theories and controversies which exist in the current literature addressing prehospital care of OHCA.

1. The configuration of prehospital critical care - This included response times, use of helicopters, physician presence and frequency of attendance at OHCA. Data analysis was based on simple descriptive statistics (absolute numbers, frequencies and mean or median values, as appropriate).

2. The effectiveness of individual prehospital critical care services - I undertook propensity score matching for each prehospital critical care service individually, compared to ALS. For efficiency's sake, this was the same process as the one used in the primary analysis, but undertaken as a subgroup analysis.

3. The presence of prehospital physicians - I undertook propensity score matching for patients attended by prehospital critical care physicians and prehospital critical care paramedics, compared to ALS. For efficiency's sake, this was the same process as the one used in the primary analysis, but undertaken as a subgroup analysis.

4. Prehospital critical care interventions - Due to the small numbers of prehospital critical care interventions identified during an interim review of the data, I only attempted simple descriptive statistics (absolute numbers and frequencies). The interventions were categorised into those delivered during OHCA and those undertaken once ROSC had been achieved. I further broke down the interventions into those undertaken in patients with: prehospital death after OHCA (this also included patients brought to the hospital without ROSC); survival to hospital arrival followed by in-hospital death; survival to hospital arrival. The aim of this stratification by outcome was to identify interventions which are likely futile or are associated only with short term survival.

5. The effect of OHCA centres - Prior to this thesis, one main theory and also particular interest of the PPI group in the qualitative research (Chapter 5) was the effect of OHCA centres on survival following OHCA. In contrast to other prehospital critical care interventions, critical care teams frequently transported their OHCA patients to OHCA centres. To examine this potential effect, I used propensity score analysis to match patients with OHCA who received care in an OHCA centre to those who received care in a non-OHCA centre. The propensity score matching process followed the same steps as described in Chapter 7, but was optimised to achieve a balance of covariates between patients transported to OHCA centres and non-OHCA centres.

8.2.7 Interpretation of results

While some of the questions and corresponding methods were already defined prior to the results of the previous chapter, others were added ad-hoc. In either case, I did not undertake sample size calculations, and these subgroup analyses are unlikely to be sufficiently powered, due to less cases being available compared to the primary analysis. Due to the phenomenon of regression to the mean, point estimates of intervention effects tend to be more extreme in smaller sample sizes, compared to larger sample sizes (Yu and Chen, 2014). Undertaking a number of analyses with small sample sizes therefore risks the possibility of finding spurious significant differences (false positives or type one error). The results presented in the following section should therefore be regarded as hypothesis-generating, rather than definitive answers.

8.3 Results

8.3.1 Configuration of prehospital critical care services

Key features of all prehospital critical care services which provided data for the analysis in this chapter and Chapter 7 are summarised in Table 8.5.

Table 8.5 Overview of key features of prehospital critical care services which provided data for the analysis in Chapter 7

	PCC-1	**PCC-2**	**PCC-3**	**PCC-4**	**PCC-5**	**PCC-6**	**Overall**
Activations	365	256	173	44	50	81	**969**
Treated*	321 (88%)	222 (87%)	155 (90%)	37 (84%)	50 (100%)	81 (100%)	**866 (89%)**
Treated per month	23	16	11	3	4	6	**10 (mean)**
Helicopter use	190 (37%)	282 (73%)	Not provided	0 (0%)	0 (0%)	91 (100%)	**563/796 (71%)**
Response time**	31min	27min	Not provided	Not provided	21min	26min	**28min**
Physician presence	327 (90%)	75 (29%)	Not provided	44 (100%)	42 (84%)	52 (64%)	**540/796 (68%)**

** Not all cases are included in the complete-case analysis in Chapter 7, due to missing data*
*** 999 call to arrival of prehospital critical care team*
PCC: Prehospital critical care service

8.3.2 Effectiveness of individual prehospital critical care services

For three of the six prehospital critical care services, the numbers of OHCAs attended and included in the complete case dataset were too small to complete a meaningful analysis of their effects on survival following OHCA (n= 16, n=33, n=39 for PCC-4, PCC-5 and PCC-6, respectively). Table 8.6 is therefore limited to those three services which attended more than 50 patients with OHCA over the study period.

Table 8.6 Results of propensity score analysis for primary and secondary outcome, stratified by individual critical care service (if n>=50), by the presence of a prehospital physician and by the use of a helicopter

Prehospital critical care	Number of matched cases Critical care	 ALS	Survival to hospital arrival	Survival to hospital discharge
PCC-1	274	805	1.78 (1.28 – 2.47)*	1.01 (0.61 – 1.68)
PCC-2	179	524	1.18 (0.76 – 1.83)	0.51 (0.22 – 1.22)
PCC-3	122	364	0.99 (0.55 – 1.79)	1.34 (0.59 – 3.04)
No physician	177	526	1.05 (0.66 – 1.66)	0.52 (0.19 – 1.41)
Physician present	355	1,037	1.88 (1.40 – 2.52)*	1.30 (0.86 – 1.95)
Rapid response vehicle	291	850	1.48 (1.08 – 2.04)*	1.39 (0.85 – 2.27)
Helicopter	233	680	1.56 (1.08 – 2.26)*	0.75 (0.41 – 1.36)

** P-value < 0.05*
PCC: Prehospital critical care service, ALS: Advanced Life Support

8.3.3 Prehospital physician presence and helicopter utilisation

The results of the subgroup analyses of prehospital critical care provided by physicians or paramedics as well as prehospital critical care teams using helicopters or rapid response vehicles are included in Table 8.6 above.

8.3.4 Prehospital critical care interventions

Prehospital critical care interventions were performed infrequently during the cardiac arrest phase of OHCA. Of 520 patients who were still in cardiac arrest on arrival of the prehospital critical care team, 203 (39.0%) received no intervention beyond the standard of ALS care. Of the three most commonly performed interventions, only one intervention (mechanical CPR (MCPR)) is a therapeutic intervention. Ultrasound is a diagnostic intervention and recognition of life extinct (ROLE) outside of the Joint Royal Colleges Ambulance Liaison Committee (JRCALC) guidelines allows for earlier termination of futile resuscitation.

After ROSC, 26.8% (80 of 299 patients) did not receive any prehospital critical care intervention. The most common interventions were prehospital anaesthesia/sedation (53%;

RSI and/or sedation/paralysis combined), the administration of IV vasopressors (31%) and bypass of the nearest hospital in favour of an OHCA centre (22%). Table 8.7 provides an overview of all interventions performed, stratified by patient groups.

Table 8.7 Prehospital critical interventions delivered during out-of-hospital cardiac arrest and after return of spontaneous circulation, stratified by patient outcomes

	Interventions during OHCA			
	Prehospital death (n=411)	**Hospital death (n=89)**	**Survivors (n=20)**	**Overall (n=520)**
Ultrasound	89 (22%)	7 (8%)	1 (5%)	97 (19%)
IV Magnesium	22 (5%)	7 (8%)	2 (10%)	31 (6%)
IV Calcium Chloride	14 (3%)	1 (1%)	0 (0%)	15 (3%)
IV Sodium Bicarbonate	22 (5%)	5 (6%)	0 (0%)	27 (5%)
Thoracostomy	4 (1%)	1 (1%)	0 (0%)	5 (1%)
ROLE outside of JRCALC	124 (30%)	N/A	N/A	124 (24%)
Mechanical CPR	155 (38%)	42 (47%)	7 (35%)	204 (39%)
Sedation and/or paralysis	7 (2%)	1 (1%)	3 (15%)	11 (2%)
	Interventions after ROSC			
	Prehospital death (n=43)	**Hospital death (n=164)**	**Survivors (n=92)**	**Overall (n=299)**
Rapid sequence induction of anaesthesia (RSI)	1 (2%)	45 (27%)	48 (52%)	94 (31%)
Sedation and/or paralysis (excluding RSI)	9 (21%)	45 (27%)	10 (11%)	64 (21%)
IV inotropes or vasopressors	14 (33%)	71 (43%)	9 (10%)	94 (31%)
IV amiodarone	2 (5%)	5 (3%)	2 (2%)	9 (3%)
IV magnesium	1 (2%)	6 (4%)	0 (0%)	7 (2%)
IV sodium bicarbonate	1 (2%)	3 (2%)	1 (1%)	5 (2%)
Electrical cardioversion	1 (2%)	3 (2%)	1 (1%)	5 (2%)
Ultrasound	1 (2%)	8 (5%)	4 (4%)	13 (4%)
Bypass of nearest hospital for OHCA centre*	N/A	38 (23%)	27 (30%)	65 of 256 (25%)

** Excluding cases of prehospital death*

OHCA: Out-of-hospital cardiac arrest, IV: Intravenous, ROLE: Recognition of life extinct, JRCALC: Joint Royal Colleges Ambulance Liaison Committee, N/A: Not applicable, CPR: Cardiopulmonary resuscitation

Other interventions performed during OHCA, but with a frequency of less than five, were surgical airway and intravenous (IV) lidocaine (once each), IV atropine (twice), thrombolysis and central venous access (three times each), double sequential defibrillation (five times). With the exception of one administration of IV atropine, all interventions were undertaken in non-survivors. Further interventions undertaken after ROSC were central venous access (once) and IV calcium (twice), all in non-survivors.

8.3.5 Out-of-hospital cardiac arrest centres

One of the potential mechanisms by which prehospital critical care could improve outcomes following OHCA is the delivery of patients to designated OHCA centres. Indeed, in the analysis in Chapter 7, 79.9% of patients who were transported to hospital after receiving prehospital critical care (234 of 293 patients) were conveyed to an OHCA centre. For patients receiving ALS care, the rate of transport to an OHCA centre was 52.9% (1,085 of 2,050 patients). Unadjusted survival rates to hospital discharge were 24.8% and 12.5% for patients transferred to OHCA centres and non-OHCA centres, respectively ($p<0.001$).

However, similarly to prehospital critical care attendance at OHCA, transport of patients to an OHCA centre was associated with better prognostic factors for survival. To adjust for this imbalance, I undertook propensity score analysis which included the same variables as the propensity score analysis described in the previous chapter, with the addition of a further variable, the time from start of resuscitation to occurrence of ROSC. As there were approximately equal number of patients admitted to OHCA centres and non-OHCA centres, one-to-one matching was used. Table 8.8 displays the results of this analysis (complete cases only).

Table 8.8 Propensity score matched cohorts of patients transferred to either a cardiac arrest centre or non-cardiac arrest centre after out-of-hospital cardiac arrest

	Non-OHCA centre (n=887)	**OHCA centre** (n=887)	***Standardised difference****
Age (median, IQR)	74 (62 - 84)	73 (61 - 82)	*7.8%*
Gender (male)	572 (64.5%)	574 (64.7%)	*0.4%*
Location of OHCA			
Public area	156 (17.6%)	160 (18.0%)	*2.5%*
Private residence	618 (69.7%)	616 (69.4%)	
Assisted living	42 (4.7%)	38 (4.3%)	
Other	71 (8.0%)	73 (8.2%)	
Aetiology			
Presumed cardiac	868 (97.9%)	866 (97.6%)	*1.5%*
Drug overdose	19 (2.1%)	21 (2.4%)	
Exsanguination	-	-	
Other	-	-	
Event witnessed			
Bystander	488 (55.0%)	499 (56.3%)	*3.1%*
EMS	205 (23.1%)	205 (23.1%)	
Not witnessed	194 (21.9%)	183 (20.6%)	
Cardiac rhythm			
Shockable	291 (32.8%)	312 (35.2%)	*5.0%*
PEA	294 (33.1%)	286 (32.2%)	
Asystole	302 (34.0%)	289 (32.6%)	
Bystander CPR			*2.7%*
Yes	655 (73.8%)	665 (75.9%)	
No	232 (26.2%)	222 (25.0%)	
AED used	24 (2.7%)	25 (2.8%)	*0.7%*
EMS response time (median, IQR)	8.1 min (5.3 – 13.0)	8.8 min (5.7 – 13.7)	*8.5%*
Prehospital critical care	53 (6.0%)	75 (8.5%)	*9.6%*
Length of resuscitation (median, IQR)	31.5 min (21.6 – 45.3)	30.6 min (21.9 – 45.9)	*9.5%*
ROSC on arrival at hospital	430 (48.5%)	471 (53.1%)	*9.6%*
Survival to hospital discharge	**107 (12.1%)**	**140 (15.8%)**	

OHCA: Out-of-hospital cardiac arrest, IQR: Interquartile range, EMS: Emergency Medical Services, PEA: Pulseless electrical activity, CPR: Cardiopulmonary resuscitation, AED: Automated external defibrillator, ROSC: Return of spontaneous circulation

The absolute treatment effect of OHCA centres on survival to hospital discharge, according to Table 8.8, can be estimated as 3.7%. However, residual imbalance of prognostic factors persists and favours outcomes in the OHCA centre group. Adjusting for this with conditional logistic regression, using all variables displayed in Table 8.8, results in an odds ratio for survival to hospital discharge of 1.48 (95%CI 0.71 – 3.12, p=0.30) when comparing survival to discharge in OHCA centres to non-OHCA centres.

8.4 Discussion

With the previous chapter demonstrating higher rates of survival to hospital arrival but no difference in rates of survival to hospital discharge associated with prehospital critical care, this chapter can be seen as the equivalent of a post-mortem examination. Why did prehospital critical care for OHCA not live up to expectations? Are there factors that can be addressed to improve effectiveness?

8.4.1 Comparing prehospital critical care services

Prehospital critical care services included in this analysis had both shared common features and features which differed between services. All services attended OHCAs regularly, particularly when compared to the frequency of exposure to OHCA amongst ALS paramedics in the United Kingdom (UK), with a median of three (interquartile range of two to five) patients with OHCA per provider per year (Benger *et al.*, 2016).

This is of particular importance, as the frequency of provider exposure to OHCA amongst ALS paramedics in Australia has been linked to higher survival rates (Dyson *et al.*, 2016). In the study by Dyson *et al.* (2016), patients treated by paramedics with a median of at least six exposures during the previous 3 years had a survival rate of 7%. This survival rate gradually and statistically significantly improved with increasing exposure of the paramedics, with survival rates of 17% for those patients treated by paramedics with over 17 exposures over 3 years. While the exact number of OHCAs attended by each individual prehospital critical care provider is difficult to assess, due to the variations in the number of providers utilised by each service, it is likely higher than 17 OHCAs over 3 years per critical care provider.

However, in contrast to the findings by Dyson *et al.* (2016), this experience of prehospital critical care providers has not translated into higher survival rates in this study. A possible explanation is that the experienced ALS paramedics in the study by Dyson *et al.* (2016) were the primary tier of the EMS response to OHCA with a median response time of 8 minutes. In contrast, median response times of prehospital critical care services in this research ranged from 21 to 31 minutes (Table 8.5). It is therefore possible that previous exposure to OHCA is an important factor for the providers who deliver early ALS, but this effect does not translate into increased survival rates when the experienced provider arrives later in the resuscitation.

Aspects where prehospital critical care services differed were the utilisation of helicopters (0% to 100%) and the involvement of prehospital physicians (29% to 100%; Table 8.5). I assessed for potential effects of these variations of individual prehospital critical care services and physician- and paramedic-delivered prehospital critical care by undertaking propensity score matching within the relevant subgroups (Table 8.6). Within the limitations of small sample sizes and the complexity of varying dispatch procedures, geography, populations and ALS responses of individual services, neither the use of helicopters nor the presence of physicians seemed to have a significant impact on overall findings (Table 8.6).

8.4.2 Prehospital critical care interventions

Breaking down prehospital critical care interventions into those undertaken during OHCA and those undertaken after ROSC reveals potential reasons as to why they seemingly do not result in better rates of survival to hospital discharge.

Firstly, as discussed in the previous section, prehospital critical care interventions during OHCA were delivered late in the resuscitation phase (Table 8.5). Secondly, most potential prehospital critical care interventions during the cardiac arrest phase of OHCA were delivered very infrequently. As shown in Table 8.7, only three interventions (ultrasound, ROLE outside of JRCALC guidelines and MCPR) were used on more than 6% of patients with OHCA.

Ultrasound was used mainly in the patient group resulting in prehospital death and was likely intended to aid the decision to stop resuscitation (Tsou *et al.*, 2017).

Recognition of life extinct (ROLE) is limited to a specific set of circumstances for ALS paramedics (Brown *et al.*, 2016). Many prehospital critical care providers can make the decision to stop resuscitation based on further information, such as the likelihood of a good outcome or patient co-morbidities. Stopping resuscitations which are deemed futile might be in the patient’s best interest, can help the grieving process of relatives and reduce resource use of both EMS systems and hospitals (Wampler *et al.*, 2012; Marco and Schears, 2002; Timmermans, 1999). What this extended competence cannot achieve, by its very nature, is an improvement in survival rates after OHCA.

The third intervention frequently performed is the use of a mechanical chest compression device (MCPR). An adequately powered randomised-controlled trial of MCPR in UK ALS paramedic practice showed no survival benefit from its use in OHCA (Perkins *et al.*, 2015c).

Similarly to prehospital critical care interventions during OHCA, only four interventions were undertaken in more than in 5% of patients where ROSC was achieved: RSI; sedation and/or paralysis; IV vasopressors; bypass of the nearest hospital in favour of an OHCA centre.

Indications for RSI, now also referred to as prehospital emergency anaesthesia (PHEA) after OHCA include a threatened airway, insufficient oxygenation or ventilation, reduced consciousness or severe agitation or the patient's anticipated clinical course (Lockey *et al.*, 2017). While there is very limited evidence and mixed results for the effects of PHEA for any prehospital condition (Cudnik *et al.*, 2010; Davis *et al.*, 2002), the theoretical argument is that RSI would be likely undertaken shortly after arrival at hospital, and optimising airway and ventilation earlier results in better outcomes for patients (Lockey *et al.*, 2017; Davis *et al.*, 2002). While prehospital RSI was the most common intervention undertaken in patients with ROSC (31%), many patients never achieve ROSC and therefore cannot attain any potential benefit from the intervention. It is therefore possible that prehospital RSI after OHCA is beneficial for only a subgroup of patients with ROSC and that the effect is not apparent in the total OHCA population attended by the critical care teams. On the other hand, it is also possible that the patients selected for this procedure by the prehospital critical care provider might have also survived with more basic airway manoeuvres followed by RSI in hospital.

The same argument can be made for the use of sedating and/or paralysing drugs which occurred in 21% of ROSC patients. This is usually done when the airway is adequately controlled by either intubation or the use of a supraglottic airway during OHCA. Once ROSC is achieved, agitation, jaw muscle spasm or inadequate/inefficient breathing can make management of the patient difficult. While these issues can be helped by giving sedative and/or paralysing drugs, the effects of these drugs on survival after OHCA have not been studied.

The intravenous administration of inotropes/vasopressors was another common OHCA intervention after ROSC (31%). Interestingly, it was most commonly used in patients who survived to hospital but died in hospital (43%) and less commonly in patients surviving to hospital discharge after OHCA (10%). A likely explanation for this can be found in the pathophysiology of the post-cardiac arrest syndrome (Pellis, Sanfilippo and Ristagno, 2015).

Cardiogenic shock is the most common cause of death in the early post-OHCA phase and is treated with inotropes and/or vasopressors (Trzeciak *et al.*, 2009). In the prehospital phase, patients with very short cardiac arrest times are often cardiovascularly stable, not requiring inotropes or vasopressors (Chalkias and Xanthos, 2012). These patients also have a very high probability of survival (Nolan *et al.*, 2008). Patients with ROSC after prolonged resuscitation on the other hand frequently suffer from cardiogenic shock (Chalkias and Xanthos, 2012).

Most patients with OHCA of longer than a few minutes will have received Adrenaline during the initial OHCA management (Soar *et al.*, 2015). This will support a labile blood pressure for a few minutes before wearing off, resulting in re-arrest and finally prehospital death (Bhardwaj *et al.*, 2017). Administering inotropes and/or vasopressors in hypotensive patients after ROSC potentially leads to patients being stable enough to be successfully transported to hospital (Hartke *et al.*, 2010). This would explain the higher rates of survival to hospital arrival observed in the prehospital critical care cohort, compared to the ALS cohort. However, it seems that these patients who survive to hospital admission with administration of inotropes/vasopressors by the prehospital critical care teams unfortunately then die later in hospital (see Chapter 7). This is possibly due to the severity of the underlying pathophysiology which caused the requirement for inotropes/vasopressors after ROSC in the first place (Nolan *et al.*, 2008).

Finally, prehospital critical care teams decided in 22% of patients with ROSC to bypass the nearest hospital in favour of an OHCA centre. Using propensity score matching, I showed that rates of survival after admission to hospital are likely higher in OHCA centres than other hospitals. The lack of statistical significance is likely due to an underpowered sample size. The effects of OHCA centres on survival have been shown repeatedly in previous research, and it is generally accepted that this should be the modern standard of care for OHCA (OHCA Steering Group, 2017; Schober *et al.*, 2016; Heffner *et al.*, 2012).

Despite this evidence supporting a positive effect of OHCA centres on survival and critical care teams transporting nearly 80% of their patients to OHCA centres, survival rates in the prehospital critical care cohort were not better than in the ALS cohort (Chapter 7). The explanation is likely to be the fact that ALS paramedics also transported over 50% of their ROSC patients to OHCA centres.

Within the prehospital critical care cohort of the primary analysis, 226 patients survived to hospital in the prehospital critical care cohort. If prehospital critical care teams transport an additional 25% of ROSC patients to OHCA centres, this translates to an additional 57 patients receiving post-OHCA care at an OHCA centre. With a generously estimated treatment effect of 3.7% absolute increase in survival associated with OHCA centres, this would translate into two additional survivors in the prehospital critical care group. Within the prehospital critical care cohort of 658 cases in the primary analysis, two additional survivors would cause an absolute difference in survival of 0.3% between the prehospital critical care and the ALS groups.

8.4.3 Theories regarding the lack of benefit from prehospital critical care for out-of-hospital cardiac arrest

It is important to stress again that the methods used in this chapter were not intended to demonstrate causation and that they are limited by small sample sizes and confounding. However, combining the results with previous research in the section above allows me to formulate a number of plausible theories that would explain the lack of overall survival benefit from prehospital critical care:

i) A significant number of patients do not receive prehospital critical care interventions.

ii) A large number of patients receiving certain prehospital critical care interventions (e.g. RSI) after ROSC might have also survived without the intervention.

iii) Some prehospital critical care interventions (e.g. inotropes/vasopressors after ROSC) prolong life but do not affect survival to hospital discharge.

iv) Some prehospital critical care interventions might be beneficial (e.g. transport to an OHCA centre) but are also achieved by ALS paramedics or undertaken too infrequently to lead to a detectable increase in survival to hospital discharge in this research.

The potential value of these theories is that they can help to shape the configuration of prehospital ALS and critical care services to optimise their effectiveness for OHCA. I will discuss this in further detail in Chapter 9.

In addition, understanding the configuration of prehospital critical care services in this research, and their interventions delivered, can also inform a further important consideration. As discussed in Chapter 7, data collection for the research in this chapter and the previous chapter has not been fully completed at the time of writing this thesis. In Appendix D2, I discuss reasons why the addition of further data to the final analysis is very unlikely to change the findings presented in Chapter 7, based on the configuration of prehospital critical care services and the frequency of interventions undertaken for patients with OHCA.

8.5 Challenges and limitations

8.5.1 Accepting the limits of data analysis

The main challenge faced in this chapter was the choice of methods of statistical analysis to address each of the different questions. In the previous chapter, I examined the singular question of survival benefit from prehospital critical care for OHCA, using variations of propensity score matching. For this chapter, I had to decide on which further questions would be useful to address, which questions could be answered with the available data, and how.

With modern computers and increasingly user-friendly statistical software, the temptation is to simply include all variables of interest in a regression model. Even the most complex model will be analysed in less than a few seconds, giving the researcher ample opportunity to refine and adjust. While this approach is not uncommon in practice (Fernandes-Taylor *et al.*, 2011), there are multiple problems with what is often referred to as data dredging (Carmona-Bayonas *et al.*, 2017).

First, in the context of this research, the decision to undertake a prehospital critical care intervention is frequently determined by factors which also determine the likelihood of survival after OHCA. As discussed in section 8.2.1, it was not possible to record all these factors for this research and, as a result, certain prehospital critical care interventions could seem falsely beneficial or harmful. Next, including a large number of interventions in one analysis risks finding statistically significant results (i.e. $p<0.05$) by pure chance (Smith and Ebrahim, 2002). If the ratio of outcome events (survival) to model variables falls below 10, regression models produce increasing erratic results (Peduzzi *et al.*, 1996). Finally, as many of the interventions of interest were only used very infrequently, findings of no effect could be entirely due to a lack of statistical power (Hsieh, Bloch and Larsen, 1998).

To avoid these issues, I limited the data analysis in this chapter to two methods – descriptive analysis and propensity score matching. Having spent much time on software programming to successfully complete propensity score matching for the previous chapter, the modifications required to adapt the process to individual prehospital critical care services, physician presence and helicopter use, was minimal. Considerably more effort was required to modify the programming to address the question of benefit from OHCA centres with propensity score matching. Given that this was a major theory of how prehospital critical care might benefit patients, and the sufficient sample size available for analysis, I considered this to be the most appropriate method. For the examination of prehospital critical care interventions, I used descriptive analysis only. The results are multiple tables (Tables 8.5 to

8.8) which are probably less intuitive to interpret than, for example, a list of odds ratios. However, this approach allows readers to assess the unadjusted data for themselves, and they can then consider if they find the resulting theories plausible or not.

8.5.2 Measuring the quality of care?

An important limitation of the data provided is that it assumes that only additional interventions have the potential to influence survival following OHCA. Due to the difficulties of measuring such a variable, the research did not attempt to assess the effect of prehospital critical care teams on the quality of (ALS) interventions during OHCA care.

Nevertheless, when transferring and cleaning data prior to analysis, I noted that prehospital critical care providers not infrequently documented subjective improvements of ongoing resuscitation through either modification or addition of ALS interventions or through better overall scene management. Due to the subjective nature of these statements and the fact that I hadn't requested this information specifically for the research, I chose not to attempt inclusion of this information in the analysis of this chapter.

Previous research has examined both the quality and frequency of ALS interventions and linked it to providers' professional background (physicians or paramedics) and level of training (Govender *et al.*, 2016; Fischer *et al.*, 2011; Olasveengen *et al.*, 2009). A recent review found no clear links between either quality or frequency of ALS interventions and provider experience, but acknowledged that most aspects of the quality of resuscitation had not been addressed (Dyson *et al.*, 2014). Given these limitations, it remains unclear if or by how much the quality of resuscitation might differ between the prehospital critical care providers and ALS paramedics in this research. Due to the lack of survival benefit from prehospital critical care shown in the previous chapter, answering this question is probably less important.

8.5.3 Data collection and completeness

Data collection differed for each prehospital critical care service which provided information on interventions delivered during OHCA care, as described in Table 8.2. While documentation of interventions in the official electronic patient records is likely fairly accurate, this might not be the case in the documentation systems which existed in parallel to the official patient records (PCC-1) particularly the paper-based system (PCC-2). Given the assumed motivation of prehospital critical care providers to demonstrate the value of their work, it is unlikely that providers would deliberately not document interventions they performed. Problems might have arisen if I had attempted to directly link interventions with survival, as providers might be more inclined to document interventions which lead to a perceived or likely positive outcome and be less detailed when documenting care which proved to be futile. Likewise, a comparison of intervention rates between prehospital critical care services might have issues of internal validity given the different documentation systems. Unfortunately, there is no system which would allow me to cross-check the accuracy of the data on prehospital critical care interventions used in this chapter. However, from personal clinical experience and based on the results obtained from the data, I would consider the possibility that inaccuracies in documentation caused a major flaw in the analysis to be very low.

8.6 Conclusions

This chapter presents, to my knowledge, the first attempt to describe in detail what prehospital critical care for OHCA is, using a combination of exploratory and descriptive analyses of prehospital critical care services and the interventions for OHCA. The findings allow us to better understand why the research in the previous chapter failed to demonstrate any benefit in survival to hospital discharge associated with prehospital critical care. Within the limitations of the methods used, it seems likely that prehospital critical care interventions are infrequently required during OHCA and might not affect survival to hospital discharge in patients that receive them after ROSC. Transporting patients to an OHCA centre is an intervention likely to have benefit in terms of survival, but this is also frequently achieved by ALS paramedics.

8.7 What next?

This chapter concludes a series of distinct, yet interlinked phases of original research examining prehospital critical care for OHCA. Each research phase helped us to understand more about certain aspects of prehospital critical care for OHCA: the current evidence; stakeholders' views; health economics; effect on outcomes and interventions delivered. I discussed the findings of each research phase in detail within the corresponding chapters.

Having created five independent pillars to support this thesis (Chapters 4 to 8), I now face the challenge of synthesising and contextualising the research findings into a comprehensive picture of prehospital critical care for OHCA. In the following chapter, I will take stock of the knowledge gained from this thesis, discuss the implications for practice and future research in this area and will attempt to address the aim at the heart of this thesis: "*to provide key stakeholders in prehospital care with the information required to guide the funding and configuration of prehospital critical care for out-of-hospital cardiac arrest, within the complex setting of mixed charity and NHS funding."*

9. Discussion and synthesis

Over the course of this thesis, I have taken the reader on a journey which led them away from the more established healthcare research settings of hospitals and outpatient clinics, into the complex world of prehospital care. The fast pace and constantly changing environment of prehospital care results in considerable limitations to the current evidence underpinning practice. The condition of interest, non-traumatic out-of-hospital cardiac arrest (OHCA), is characterised by a very high immediate mortality rate and the need for life-saving treatments within seconds to minutes. The current standard of care for OHCA in the United Kingdom (UK) is Advanced Life Support (ALS), provided by paramedics. Prehospital critical care teams are also sent to patients with OHCA in some regions, and they might improve survival through additional interventions which are not currently part of the ALS treatment protocol.

When I began the planning for this thesis, there was little evidence to support any of these interventions or the concept of prehospital critical care in general. On this background, I embarked on five distinct research phases, each addressing one of the objectives listed in Chapter 2. In this chapter, I will first review the main findings of each chapter before combining them in an attempt to address the main questions posed at the beginning of the thesis. While the discussion sections contained within each of the chapters focus specifically on the research presented in the chapters, this synthesis will focus on the implications of the combined research results on prehospital care for OHCA.

9.1 New knowledge and dissemination of results

At the beginning of this thesis, prehospital critical care was a promising but undefined and unproven intervention which might improve survival following OHCA. During the planning phase of the research, it became clear that many aspects of prehospital critical care for OHCA were based on hypothesis and opinion, rather than evidence. I hope the reader will agree that, after a systematic review of the literature and four original research projects, prehospital critical care for OHCA has been examined and demystified. These findings have the potential to directly influence funding, policy and practice in prehospital care for OHCA.

This section provides an overview and reminder of the key findings of the research presented in Chapters 4 to 8. Appendix E1 contains a critical reflection on the corresponding methods.

At the start of the doctoral research fellowship, I presented my research plans at the 2016 Annual Meeting of the Society of Intensive Care of the West of England and the Postgraduate Research Conference, Health and Applied Sciences, University of the West of England, winning the prize for best oral presentation at both. The corresponding research protocol was published in BMC Emergency Medicine (von Vopelius-Feldt *et al.*, 2016) and the manuscript of this can be found attached to the hardcopy of this thesis.

9.1.1 Systematic review of the literature

The systematic review provided important information on the quantity, quality and results of the current literature on prehospital critical care for OHCA. It also highlighted important issues of research design. With only six full-text publications comparing prehospital critical care to ALS care for OHCA through observational research methods, the review confirmed a lack of strong evidence supporting prehospital critical care. Within each included study, imbalances of important prognostic factors favoured survival in the prehospital critical care groups, requiring adjustment of results through statistical methods.

Once adjustment was achieved through either subgroup analysis, multiple regression or propensity score analysis, three publications demonstrated an association between prehospital critical care and higher survival rates, while three publications showed no difference. Where no benefit was shown, studies were considerably underpowered to detect important differences in survival rates after OHCA.

For the three publication which did show a benefit from prehospital critical care for OHCA, limitations were potentially unmeasured confounding, the effects of dispatch and stand-down procedures of prehospital critical care and the effects of transporting patients to OHCA centres. In summary, the review confirmed the need for further research and identified factors threatening the internal validity of observational research in this field, which informed the design of my own research.

The review has been presented as a poster at EMS2018 Copenhagen and as an oral presentation at the Annual Meeting 2018, Society of Intensive Care of the West of England. I submitted a manuscript which was peer reviewed and has been published in Resuscitation (von Vopelius-Feldt, Brandling and Benger, 2017). The published manuscript can be found attached to the hardcopy of this thesis.

9.1.2 Stakeholders' views on research, randomisation and funding

After disagreement amongst some stakeholders was noted during the planning phase, qualitative methods allowed me to formally map the views of relevant stakeholder groups, identify reasons for disagreements and also common underlying concepts. The five stakeholder groups identified for the research comprised patient and public involvement (PPI), air ambulance charities, prehospital commissioners, researchers and prehospital critical care providers.

All groups were supportive of prehospital research, but their approach and priorities differed due to each group's unique context. When it came to randomisation of prehospital critical care, issues of reputational risks were important for charities and providers. The PPI group considered randomisation to be unethical, due to their perception that prehospital critical care must be highly beneficial, and the unique situation of suspended life presented by OHCA. Commissioners and researchers did not consider prehospital critical care or OHCA as uniquely different from other interventions or conditions and were more concerned with the perceived high costs and the validity of research, respectively. Finally, stakeholders were also in disagreement about the role of research in funding decisions. The PPI and charity groups demonstrated willingness to accept observational research, supplemented with common sense and social acceptability. Prehospital critical care providers were concerned about the impact of a withdrawal of funding on their professional identity and day to day work. For researchers, quality of research was a key aspect of funding decisions, as observational research had led to poorly invested funds before. Commissioners on the other hand felt that opportunity costs were an important issue, as any funding directed towards prehospital critical care would mean less funding for other important services.

Taken together, the varying approaches of stakeholders to research in general, randomisation of prehospital critical care for OHCA and the role of research in funding processes meant that no consensus could be identified in regards to the ideal research design for this thesis. However, despite the strong opposing views on some of the subjects, I was able to identify common values underlying all stakeholders' strategies. Progress through scientific research was appreciated by all stakeholders, despite each group focusing on different aspects. All stakeholder groups, at some point during the discussions, referred to achieving fairness, which was interpreted either as vertical or horizontal equity. Finally, the common value of helping unwell people was a common guiding value, which again was interpreted differently, depending on the stakeholders' backgrounds.

This research provided a detailed description of stakeholders' views, the mechanisms which led to these convictions, and common values which can be used in the future to move towards consensus in regards to prehospital critical care and OHCA or other similar healthcare settings. I presented this research as a poster at EMS2018 Copenhagen and published it in Health Science Reports (von Vopelius-Feldt, Brandling and Benger, 2018). The corresponding manuscript can be found attached to the hardcopy of this thesis.

9.1.3 The costs of prehospital care for out-of-hospital cardiac arrest

I used a combination of my own data on the costs of prehospital critical care and ALS as well as data from published research on downstream costs to create a decision analysis model of prehospital critical care or ALS as treatment for OHCA. This allowed me to estimate the total costs of the OHCA pathway from prehospital care to post-discharge and the minimally economically important difference in survival required for prehospital critical care to be cost-effective.

Based on these data, the estimated costs of prehospital ALS for OHCA is £347. The incremental cost of a helicopter-based prehospital critical care team is £1,711 per OHCA attended. The biggest cost occurs during ICU stay, from complex interventions undertaken in survivors of OHCA and long-term care in survivors with poor neurological recovery.

When considering all costs occurring along the OHCA pathway, prehospital ALS is cost-effective at an estimated £11,407 per QALY (quality-adjusted life year) with an interquartile range of £6,840 per QALY to £16,863 per QALY. Using a willingness-to-pay threshold of £20,000 per QALY and a range of rates of survival to hospital arrival and survival to hospital discharge, I estimated that, in order to be cost-effective, prehospital critical care would need to achieve at least a 4% absolute improvement in survival rates follow OHCA.

I presented this research at the South West Emergency Academic Team Meeting 2018 and submitted a manuscript for peer review and publication. The submitted manuscript can be found attached to the hardcopy of this thesis.

9.1.4 The effect of prehospital critical care on survival following out-of-hospital cardiac arrest

In Chapter 7, I examined the effects of prehospital critical care on short and longer-term survival following OHCA, which also provided insights into the effects of dispatch methods and the cost-effectiveness of prehospital critical care.

After combining a prospectively created database of prehospital critical care for OHCA with data from the national OHCAO database, I was able to analyse cohorts of 7,149 and 866 patients receiving ALS and prehospital critical care, respectively. The corresponding unadjusted rates of survival to hospital discharge were 8.7% and 12.8% but, as predicted, positive prognostic factors were significantly more frequent in the prehospital critical care group.

Balancing prognostic factors through propensity score matching in cases with complete datasets resulted in matched cohorts of 1,847 and 658 cases of OHCA receiving ALS and prehospital critical care, respectively. Rates of the secondary outcome of survival to hospital arrival were 27.7% and 34.4% in the ALS and prehospital critical care cohort, but 11.9% in both groups for the primary outcome of survival to hospital discharge. Using conditional logistic regression to account for any remaining imbalance resulted in an odds ratio of 1.06 (95% confidence interval 0.75 to 1.49) for survival to hospital discharge when comparing prehospital critical care with ALS. These results remained stable in a subgroup analysis (witnessed, shockable OHCA only) and two sensitivity analyses (primary dispatch of prehospital critical care and multiple imputation dataset).

After combining these data with the decision analysis model in Chapter 6, prehospital critical care was very unlikely to be cost-effective even at higher willingness-to-pay thresholds, including in one-way sensitivity analyses which varied the costs of prehospital critical care or its effect on good neurological outcome in survivors of OHCA. This research provides the largest dataset to examine the benefits of prehospital critical care for OHCA in the UK and probably the most thoroughly adjusted analysis undertaken to date. A manuscript of this research will be submitted for peer review and publication, once completed.

9.1.5 Prehospital critical care interventions for out-of-hospital cardiac arrest

The final research phase was dedicated to an analysis of prehospital critical care services and the interventions used during OHCA care. Using a number of different analysis strategies, I was able to further define prehospital critical care for OHCA and to generate hypotheses regarding its lack of effect on survival after OHCA.

Prehospital critical care overlaps with helicopter use (HEMS) and prehospital physician involvement, but there was no evidence that either had an effect on survival to hospital discharge after OHCA. Prehospital critical care providers are frequently exposed to OHCA but, possibly due to their relatively late arrival on scene (median 28min, compared to 7min for the first ALS resource), this experience did not translate into clinical benefit.

Prehospital critical care interventions are not frequently undertaken during the cardiac arrest phase (39.0% of patients did not receive any additional intervention beyond ALS procedures), and the interventions which are undertaken most frequently have either been shown to be non-beneficial (mechanical chest compressions) or are non-therapeutic (ultrasound and early cessation of resuscitation). The frequency of prehospital critical care interventions is higher if return of spontaneous circulation (ROSC) is achieved, with 26.8% of patients with ROSC receiving no critical care intervention. Prehospital anaesthesia or sedation are the most frequently undertaken interventions however, given the lack of overall benefit from prehospital critical care, it is possible that the patients receiving the interventions would also have survived without it. Intravenous inotropes or vasopressors are also used frequently, but are more common in patients surviving to hospital and are then followed by in-hospital death. A possible explanation is that the intervention can stabilise patients until they arrive in hospital, but the underlying pathophysiologic insult is too severe and in-hospital death ensues.

In a propensity score analysis, treatment of patients at a dedicated OHCA centre seems to be associated with higher survival to hospital discharge. However, OHCA centre conveyance also occurs in over 50% of patients in the ALS paramedic cohort (compared to nearly 80% in the prehospital critical care cohort). A manuscript of this research will be submitted for peer review and publication, once completed.

9.2 Decision-making under uncertainty

Having summarised the key findings and knowledge gained over the course of the previous chapters, it is now worth reconsidering the aim of the thesis, stated in Chapter 2.

> *"The aim of this thesis is to provide key stakeholders in prehospital care with the information required to guide the funding and configuration of prehospital critical care for OHCA, within the complex setting of mixed charity and National Health Service (NHS) funding."*

In other words, I hope that the results summarised in the previous section will help charity and NHS funders and clinicians to make decisions about prehospital critical care for OHCA and about the configuration of such services. A key aspect of such decision making is certainty

(National Institute for Health and Care Excellence, 2013). How certain are we about the findings and results presented, and how certain can we be about implementing them? In this section I will assess the certainty of the findings of the thesis from different perspectives, before reviewing the potential choices available to stakeholders in prehospital critical care and OHCA.

9.2.1 Statistical measures of effects and uncertainty

Traditionally, a p-value of less than 0.05 is considered to be the defining cut-off at which a research finding becomes statistically significant and the effect associated with the intervention studied is accepted to be true (Colquhoun, 2017). Applying this approach of statistical significance to the results of my primary analysis would translate into: there was no association with the primary outcome of survival to hospital discharge (p=0.75); there was a significant (p=0.005) association between prehospital critical care attendance at OHCA and the secondary outcome of survival to hospital arrival. This interpretation and use of the p-value, while still widespread in the medical literature today, has a number of limitations.

Firstly, an increasing number of research findings manage to attain p-values of just below 0.05 and are therefore accepted as significant (de Winter and Dodou, 2015). Further research frequently fails to reproduce such findings (Allison, Shiffrin and Stodden, 2018). At the same time, some authors refer to results with p-values just larger than 0.05 as "*marginally significant"* or *"approaching significance"* (Pritschet, Powell and Horne, 2016; Hankins, 2013). Hankins (2013) provides an exhaustive and entertaining list of linguistic attempts to attribute significance to p-values between 0.05 and 0.10. Another limitation of the exclusive focus on p-values is that they do not contain information on the precision of the estimate of treatment effect sizes (Amrhein, Korner-Nievergelt and Roth, 2017). Neither do they contain information about confounding or bias in the research methods or the adequacy of the sample size (Amrhein, Korner-Nievergelt and Roth, 2017; Ioannidis, 2005).

This combination of shortcomings of using p-values in the interpretation of medical research has led to increasing criticism of this approach (Colquhoun, 2017; Fernandes-Taylor *et al.*, 2011). The somewhat provocative title of the publication by Ioannidis (2005), which addresses the issues of p-value interpretation, is worth citing in full: *Why most research findings are false.* A more careful approach to p-values, as suggested by Amrhein, Korner-Nievergelt and Roth (2017), applied to the primary analysis of this thesis, would be to say that:

- There is no evidence against the null-hypothesis of no association between prehospital critical care and the primary outcome of survival to hospital discharge (p=0.75).
- There is strong evidence against the null-hypothesis of no association between prehospital critical care and the secondary outcome of survival to hospital arrival (p=0.005).

One approach to describing results of quantitative research findings, which addresses some of the short-comings of the p-value, is to use the point estimate and distribution of the treatment effect (Amrhein, Korner-Nievergelt and Roth, 2017). The point estimate can be seen as the most likely estimate of the effect of the intervention studied, while the lower and upper 95% confidence interval are interpreted as worst and best case scenarios. In Table 9.1, I apply this approach to the main findings from this thesis. While the primary analysis provided odds ratio, these have been criticized as being non-intuitive to interpret. I therefore calculated absolute treatment effect values from these odds ratios, assuming rates of 27.7% and 11.9% for survival to hospital arrival and survival to hospital discharge, respectively, (taken from the matched ALS cohort of the primary analysis). A further format recommended to improve the interpretation of effectiveness of therapeutic interventions is the number of patients needed to treat (NNT) to achieve one outcome of interest. Table 9.1 shows point estimates and 95% confidence intervals for primary and secondary outcome of survival to hospital discharge and survival to hospital arrival, in odds ratio, absolute treatment effect and NNT format.

Table 9.1 Odds ratios, absolute treatment effects and numbers needed to treat estimations for prehospital critical care for out-of-hospital cardiac arrest, compared to Advanced Life Support, based on the primary analysis in Chapter 7

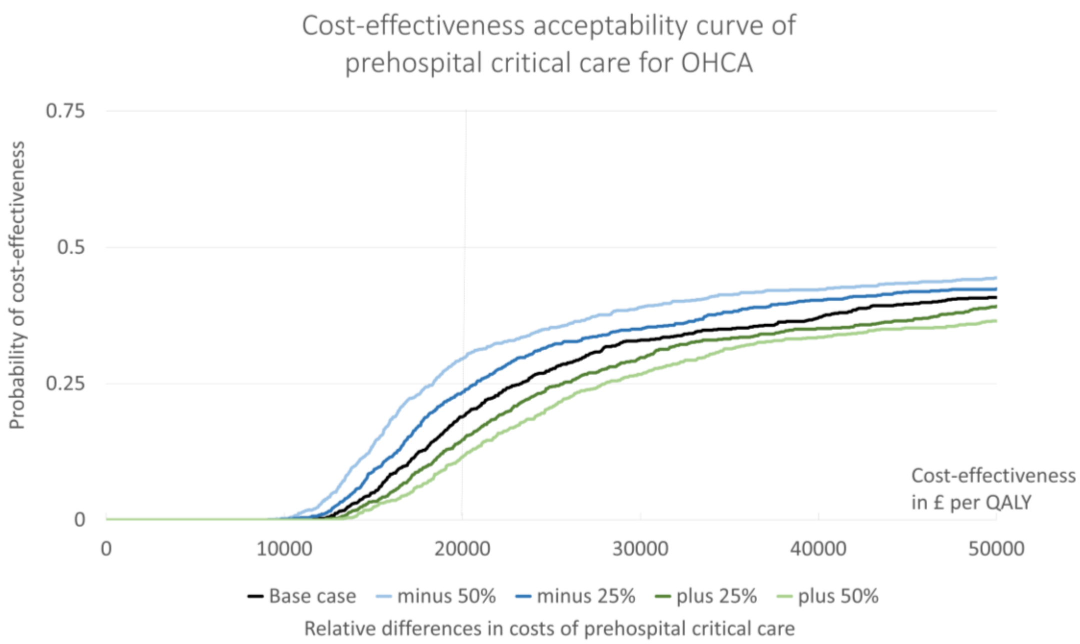
		Most likely estimate	**Worst case estimate**	**Best case estimate**
Survival to hospital discharge	*Odds ratio*	**1.06**	0.75	1.49
	*Absolute treatment effect**	**0.7%**	-3.1%	5.5%
	*Number needed to treat**	**143 patients**	*(harmful intervention)*	19 patients
Survival to hospital arrival	*Odds ratio*	**1.39**	1.10	1.75
	*Absolute treatment effect**	**9.7%**	2.7%	17.2%
	*Number needed to treat**	**11 patients**	37 patients	6 patients

**calculated from the corresponding odds ratio*

The advantage of the format of results presented in Table 9.1 is that stakeholders can draw their own conclusions about what effect size and what degree of certainty they consider sufficient to adopt a new intervention. Using the NNT allows intuitive comparison of treatments and facilitates explanation of research findings to lay people.

Finally, I combined the uncertainty included in the 95% confidence intervals of clinical effectiveness with the uncertainty of cost estimates in a decision analysis model, using probabilistic sensitivity analysis. The cost-effectiveness acceptability curves presented in Chapters 6 and 7, and reproduced here for illustrative purposes (Figure 9.1), are designed to support stakeholders in decision making under conditions of uncertainty (Gray *et al.*, 2011).

Figure 9.1 Reproduction of cost-effectiveness acceptability curve of prehospital critical care for out-of-hospital cardiac arrest, originally Figure 7.10 in Chapter 7



OHCA: Out-of-hospital cardiac arrest

Stakeholders can select a willingness-to-pay threshold (WTP), or a range of these, and the cost-effectiveness acceptability curve will provide a probability between 0 and 100% that the intervention is cost-effective at this WTP (Gray *et al.*, 2011). Rather than providing a dichotomous yes/no answer to the question of cost-effectiveness, this approach allows stakeholders to also incorporate other factors into their decision making, which is something the majority of the stakeholders in Chapter 5 suggested.

For example, in the context of clear public demand and available resources, a probability of cost-effectiveness at the chosen WTP of, for example, 60% might be considered to be sufficient to fund a new intervention. In contrast, if funding is very constrained and the data underlying the cost-analysis model is susceptible to bias or confounding, a higher probability of cost-effectiveness of, for example, 90% might be desirable. In regards to prehospital critical care for OHCA, whichever additional factors stakeholders might want to consider in their decision making process (see Chapter 5), the probability of cost-effectiveness of prehospital critical care only just exceeds 50% in one of the sensitivity analyses considered (Chapter 7).

In summary, prehospital critical care is associated with a moderate to large effect on the secondary outcome of survival to hospital arrival after OHCA. For the primary outcome, the most likely estimate is a very small positive association between prehospital critical care and survival to hospital discharge. The range of possible effects on the primary outcome include both moderate harm and benefit associated with prehospital critical care. For cost-effectiveness, prehospital critical care is unlikely to be cost-effective at any WTP threshold. An important limitation to all interpretations of results discussed in this chapter is the assumption that the underlying data are free from bias or confounding. In the next section, I will discuss whether this assumption can be considered to be true.

9.2.2 Robustness of the statistical analysis

In Chapter 4 (systematic review) and Chapter 7 (survival analysis) I discussed in detail the fact that prehospital critical care teams, on average, attend patients with better prognostic factors, compared to their ALS paramedic colleagues. These measured confounders will ideally have been fully adjusted for by the propensity score matching process (Guo and Fraser, 2010). Table 7.8 (Chapter 7) gives readers the opportunity to assess for themselves if the matching resulted in a sufficient balance of prognostic factors. I would argue that a slight imbalance remains, with more favourable distribution of the variables Utstein location and cardiac rhythm in the prehospital critical care cohort. On the other hand, Emergency Medical Services (EMS) response time is slightly shorter in the ALS paramedic cohort. After using a further adjustment process, conditional logistic regression, I am confident that the resulting odds ratios presented in Table 9.1 have been fully adjusted for all measured confounding (Funk *et al.*, 2011).

Also in Chapter 7, I discussed the issue of unmeasured confounding and the potential of propensity score matching to partially adjust for this (Holmes, 2014). Of course the major flaw in this argument is that, by definition, it is impossible to measure if or how much unmeasured confounding has indeed been adjusted for (Austin, 2011a).

I therefore decided to run a simulation of unmeasured confounding within my dataset. To do this, I undertook the primary analysis as described in Chapter 7 but excluded bystander cardiopulmonary resuscitation (CPR) from the model. Bystander CPR is therefore a known but, as far as the analysis is considered, unmeasured confounder. Table 9.2 shows the distribution of bystander CPR in the original unmatched cohort, in the propensity score matched cohorts of the original analysis and in cohorts matched through propensity score with bystander CPR excluded from the propensity score.

Table 9.2 Rates of cardiopulmonary resuscitation by bystanders: in the original unmatched cohort; in the propensity score matched cohorts of the original analysis; in cohorts matched through propensity score, where bystander cardiopulmonary resuscitation was excluded from the propensity score

	ALS	**Prehospital critical care**	***Absolute difference***
Original cohorts	72.9%	79.5%	*7.3%*
Propensity score matched (full model of primary analysis)	79.4%	79.2%	*-0.2%*
Propensity score with bystander CPR as unmeasured confounder	75.1%	79.2%	*4.1%*

ALS: Advanced Life Support, CPR: Cardiopulmonary resuscitation

As shown in Table 9.2, full propensity score matching achieved a reduction in the imbalance of the variable bystander CPR between the ALS and prehospital critical care groups from 7.3% to -0.2%. If bystander CPR hadn't been measured, the imbalance of the unmeasured variable bystander CPR would have still been reduced to 4.3%, through propensity score matching on all the other measured variables. This is achieved through a correlation between bystander CPR and other variables, such as cardiac rhythm. Decreasing the difference in the variable cardiac rhythm also decreased the difference in the variable bystander CPR between the two cohorts.

It is important to emphasise that this adjustment process of unmeasured confounders depends on a positive correlation between measured and unmeasured confounding (i.e. influencing the results in the same direction) and the strength of the association (a stronger association between measured and unmeasured variables results in better adjustment) (Guo and Fraser, 2010). As discussed in more detail in Chapter 7, based on theoretical arguments and previous research, most potential unmeasured confounders in the context of prehospital critical care for OHCA are likely to fulfil the criteria of positive association with measured confounders. For example, co-morbidities (unmeasured) are associated with advanced age (measured). Both will be more frequently present in the ALS cohort, with likely negative effects on survival rates (Granfeldt *et al.*, 2017; Martinell *et al.*, 2017; Prince *et al.*, 2015).

In addition to the issue of unmeasured confounding, I also demonstrated in Chapter 7 that stand-downs of prehospital critical care team or requests from ALS paramedics to dispatch a critical care team influence the apparent effect on survival. In the sensitivity analysis which excluded stand-downs and secondary dispatch of prehospital critical care to OHCA, the odds ratios for both primary and secondary outcome were lower than in the primary analysis (Chapter 7, Tables 7.7 and 7.8). Given the potential bias from unmeasured confounding and dispatch procedures discussed in this section the statistical estimates of effect size and uncertainty should be supplemented by a further caveat: the results presented potentially overestimate positive effects of prehospital critical care on outcomes after OHCA to a degree. This bias is likely small but impossible to quantify exactly.

A further argument supporting the validity of the statistical analysis is the fact that a clear benefit of survival to hospital arrival was shown for prehospital critical care but without a benefit on survival to hospital discharge. This suggests that the approach I used is capable of identifying benefit where it exists, but that the prehospital critical care has no to little effect on the primary outcome of survival to hospital discharge.

These findings of increased rates of survival to hospital arrival but not survival to hospital discharge are also clinically plausible. In Chapter 8, I analysed interventions undertaken by prehospital critical care teams during their care for patients with OHCA. I've shown that particularly the use of vasopressors/inotropes after ROSC by prehospital critical care providers might allow patients to survive to hospital arrival but then die in hospital. A similar effect was found in the recently published randomised trial of Adrenaline (an inotrope) during OHCA (Perkins *et al.,* 2018). Significant short term benefits in the form of survival to hospital arrival were observed in the Adrenaline arm, compared to placebo (absolute improvement 15.8%). However, this benefit from Adrenaline during OHCA was reduced considerably for the outcome of survival to hospital discharge (absolute improvement 0.8%, $p=0.02$) and disappeared when comparing survival with favourable neurological outcome (absolute improvement 0.3%, $p>0.05$) (Perkins *et al.,* 2018).

Despite the uncertainty introduced by the limited sample size of the observational research in Chapter 7 and potential for remaining confounding, prehospital critical care is almost certainly not cost-effective, as demonstrated in the economic analyses in Chapter 6 and Chapter 7. The combination of higher rates of survival to hospital admission with at best minimal improvements in survival to hospital discharge associated with prehospital critical care result in considerably increased costs with little to no gains in effectiveness.

9.2.3 Summary

After providing an estimate of the treatment effect and cost-effectiveness of prehospital critical care on survival following OHCA, including estimates of certainty and potential bias in the underlying data, stakeholders are now faced with a number of potential decisions:

- To gather more information before making any changes to prehospital critical care for OHCA;
- To start, stop or continue funding prehospital critical care for OHCA;
- To consider funding other aspects of the Chain of Survival for OHCA.

I will address the first two points in the following sections. The third point is an important aspect of a general aspiration to improve prehospital care for OHCA, but is not included in the aim of this thesis. I will therefore review the Chain of Survival in UK prehospital care in Appendix E2.

9.3 The value of further research

Rather than making an immediate decision based on the evidence provided here, stakeholders should consider the potential value of further research first. This should be a directed process, with any further research clearly addressing outstanding issues which would actually change stakeholders' decision-making. Both further research and maintaining the status quo of prehospital critical care for OHCA comes with potential opportunity costs, which should be weighed up against the potential benefits of more research. The analysis of associations between prehospital critical care and survival rates after OHCA presented in Chapter 7 contains a number of limitations. These can be examined regarding the value of further research to address them.

9.3.1 Do we need a randomised controlled trial of prehospital critical care for out-of-hospital cardiac arrest?

The issue of randomised controlled or observational research design has been a central theme of this thesis. From the very first informal discussions during the planning phase, through funding application and the analysis of stakeholders' views in Chapter 5, randomisation of prehospital critical care has divided opinions and evoked strong reactions. Table 9.3 gives an overview of stakeholder groups' views on randomisation of prehospital critical care for OHCA and their central arguments supporting these views.

Table 9.3 Stakeholders' views on randomisation of prehospital critical care for out-of-hospital cardiac arrest, and underpinning arguments

Stakeholder group	View on randomisation	Main argument
Patient and public involvement group	Strongly against	Perceived benefit from prehospital critical care and the imminence of life-or-death during out-of-hospital cardiac arrest
Air ambulance charities	Largely against	Reputational concerns; mission statements of helping people in need difficult to align with randomisation
Prehospital commissioners	Against	Perceived opportunity costs of randomising an expensive intervention only applicable to a small group of patients
Prehospital researchers	Strongly supportive	Concerns about observational data being biased in favour of the intervention and potentially misleading
Prehospital critical care providers	Equivocal	Participating in high quality research resonates with professional identity. Not attending patients as part of randomisation in conflict with professional identity

An interesting aspect of the results of Chapter 7 (survival analysis) is that they can be used as counter-arguments to the more strongly expressed stakeholder views. The PPI group were very concerned that the training and experience of ALS paramedics might not be sufficient to provide safe and effective care for OHCA, particularly the transfer of patients to OHCA centres following ROSC for further treatment. Given the equal rates of survival to hospital discharge in the propensity score matched cohorts (11.9% in both ALS and prehospital critical care groups) and over 50% of patients with ROSC being transferred to OHCA centres in the ALS paramedic group, these concerns can be reduced.

On the other hand, the main concern of prehospital researchers regarding the observational research design was the notion that it would falsely show benefit from prehospital critical care for OHCA, due to confounding and bias. In the previous section, I explained that measured confounding has been fully adjusted for, but some potential for unmeasured confounding remains, favouring prehospital critical care. With no evidence for an effect of prehospital critical care on the primary outcome of survival to hospital discharge, the concerns about a spurious positive outcome, which then gets reversed in a randomised controlled trial (RCT), are largely irrelevant.

As a result of this thesis, a carefully designed RCT, likely using cluster-randomisation, would certainly be more feasible to accept amongst stakeholders. Complete elimination of any residual bias, present in the observational data of this thesis, would reduce some of the resulting uncertainty of the point estimate of effectiveness (Concato, Shah and Horwitz, 2000). Randomisation would also allow for a causal statement about the effects of prehospital critical care on survival following OHCA, under the counterfactual framework (Rubin, 2005). However, as discussed in Section 9.2.2, it is unlikely that the result of an RCT of prehospital critical care for OHCA will reverse the findings of this observational research.

Reassuringly, there is also broader support for the idea that the results of observational and randomised controlled research are actually not that dissimilar. A meta-analysis published in the Cochrane Database of Systematic Reviews compared findings between observational and randomised research across a wide range of study designs and healthcare interventions (Anglemyer, Horvath and Bero, 2014). Of 14 systematic reviews included in the meta-analysis, 11 found no difference between observational studies and RCTs. One review found observational studies to have larger effect sizes, while two reviews found smaller effect sizes, compared to RCTs. The pooled odds ratio comparing effects from RCTs with observational research was 1.08 (95%CI 0.96 to 1.22) (Anglemyer, Horvath and Bero, 2014). With the annual costs of a prehospital critical care service in the range of £2 million (Chapter 6), an RCT would require substantial funds, which may prove too high to be justifiable.

9.3.2 Sample size, outcomes and interventions

Independent of observational or randomised research designs, further research could expand on a number of aspects. In Chapter 7, I discussed the question of whether the research should be repeated with a larger sample size. The conclusion I drew in Chapter 7 was that a larger sample size would be unlikely to change the results significantly, i.e. shifting the p-value from above to below the threshold of 0.05. Having now presented the results of the primary analysis in other formats (see Table 9.1), I will revisit the potential benefit of a larger sample size in reducing uncertainty (Wan *et al.*, 2014).

The current 95% confidence interval for the absolute effect of prehospital critical care on survival to hospital discharge following OHCA is -3.1% to +5.5%. As some of the potential implications of this result might be heavily contested, narrowing the confidence interval would be useful for the decision-making process. However, one would need to balance the benefit of a larger study against the costs of undertaking it. Even with the current, relatively wide, 95% confidence interval, the economic analysis is fairly clear in its conclusion that prehospital critical care is unlikely to be cost-effective for OHCA, due to higher costs, when compared to ALS prehospital care.

A similar argument can be made for further research using quality of life or good neurological recovery as the primary outcome, rather than just survival to hospital discharge. It is possible that prehospital critical care has no effect on survival rates, but, through interventions such as prehospital anaesthesia and haemodynamic optimisation, improves neurological or functional recovery in survivors. In my study, only 11.9% of patients receiving prehospital critical care survived to hospital discharge, meaning almost 90% of patients would not be able to benefit from a potential effect on functional outcomes. Furthermore, in more recent years in the UK, good quality of life is already achieved in the majority of survivors of OHCA who received ALS prehospital care (Benger *et al.*, 2016; Gates *et al.*, 2017). Any effect of prehospital critical care on quality of life and functional outcomes after OHCA would therefore be minimal at most. I included a sensitivity analysis of the rate of good neurological recovery (Cerebral Performance Score, CPC 1 or 2) in the economic analysis in Chapter 7 (Figure 7.11). Even if a considerable increase in CPC1-2 in survivors of OHCA receiving prehospital critical care was observed, the probability of cost-effectiveness would still only just exceed 50%.

Another potential focus for further research would be individual prehospital critical care interventions. It is certainly possible that the lack of overall benefit associated with prehospital critical care in this thesis is due to clinically effective interventions being undertaken too infrequently to demonstrate benefit within this sample size.

In Chapter 8, I describe how, during OHCA, the three most common interventions undertaken are either non-therapeutic (ultrasound and cessation of resuscitation) or have been shown in a randomised trial to be non-effective (mechanical chest compressions) (Jentzer *et al.*, 2016; Perkins *et al.*, 2015c). In regard to interventions undertaken after ROSC, prehospital anaesthesia or sedation, the use of vasopressors or inotropes and bypassing the nearest hospital in favour of an OHCA centre would be interventions of interest for further research. Given that these interventions only apply to the proportion of patients with OHCA who receive ROSC and are only delivered in a subset (Table 8.7, Chapter 8), achieving adequate sample sizes would be a major challenge. One potential solution would be, rather than limiting the interventions and research to prehospital critical care teams, to utilise selected ALS paramedics to deliver the interventions. Advantages and disadvantages of this potential approach are discussed in more detail in Section 9.4.

In summary, in regard to the research question of the clinical and cost-effectiveness of prehospital critical care for OHCA, further research would likely reduce uncertainty but is unlikely to significantly change the overall results.

9.4 Funding of prehospital critical care for out-of-hospital cardiac arrest

This section addresses the key question which the thesis aimed to answer: should prehospital critical care for OHCA be funded by the NHS? With no indication of better outcomes from prehospital critical care but considerably higher costs compared to the standard of ALS paramedic care, the short and sobering answer would be no. However, as explained in the introduction to this thesis and further explored in the qualitative research in Chapter 5, this is a complex intervention in a complex environment, applied to a condition with often dramatic impact on survivors and relatives. It is therefore worth going through steps to be considered before reaching an answer, which I will do in this section.

9.4.1 Is there a need to improve prehospital care for out-of-hospital cardiac arrest?

A central value underlying stakeholders' approach to the subject of prehospital critical care for OHCA, identified in Chapter 5, was fairness or equity. With a mortality rate of 91.3% from OHCA in this study, it is understandable that some stakeholders, such as the PPI group, would perceive the current treatment of OHCA as insufficient and therefore unfair when compared to other disease conditions. In fact, the group argued that OHCA funding should, if anything, be higher than for other less immediately life-threatening conditions, which I identified as an argument of vertical equity (Mooney, 2000).

As described in the Introduction Chapter, a considerable proportion of OHCAs are due to either acute or underlying chronic irreversible pathophysiological processes and therefore not currently amenable to any therapy (Nichol and Baker, 2007). The question is therefore whether prehospital critical care in the UK could and should be improved, or if the current low survival rates are merely a reflection of the underlying disease processes.

While comparing outcomes between healthcare systems is fraught with difficulties (Nishiyama *et al.*, 2014), it can help to at least partially assess the potential impact of attempts to improve prehospital care in the UK. The recommended method of comparing OHCA outcomes across healthcare systems is the rate of survival to hospital discharge in patients with witnessed OHCA and a primary rhythm of ventricular fibrillation (VF); the Utstein comparator group (Perkins *et al.*, 2015a).

One of the EMS systems considered to be most effective in the care of OHCA patients worldwide is based in King County, United States of America (USA) (Sudden Cardiac Arrest Foundation, 2014). In 2016, King County EMS reported rates of survival to hospital discharge in the witnessed VF OHCA group of 54% (Public Health - Seattle & King County, 2016). This compares to rates of survival to hospital discharge after witnessed VF OHCA in this study of 25.7%; less than half of what is achieved in King County. Of note, EMS systems in Europe have also reported survival rates in this patient cohort of approximately 50% (Mauri *et al.*, 2016; Lindner *et al.*, 2011). The mechanisms by which the King County and other systems achieved these results are further discussed in Appendix E2. For now, the comparison of survival rates in the Utstein comparator group shows that there is indeed considerable potential and need for improvement in the EMS response to OHCA in the UK.

9.4.2 How much are we willing to spend?

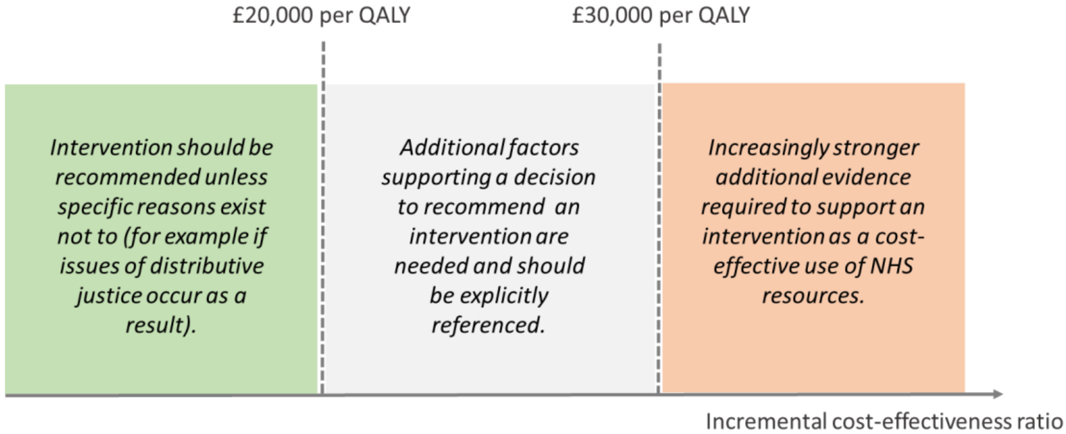
As for most things in life, improving prehospital care for OHCA is unlikely to be achievable without increasing resources in the form of money spent. Two important questions are therefore whether there should be a spending limit or WTP threshold, and how it should be defined.

In Chapter 5, the PPI group were very uncomfortable with the notion that in the life-or-death situation of OHCA, anything but the best care might be delivered as a result of an ongoing research project. This was in keeping with the principle of the Rule of Rescue (Cookson, McCabe and Tsuchiya, 2008). On the other hand, the group did not apply the Rule of Rescue to limitations of funding and seemed to accept a reality where resources were limited, as long as they were fairly distributed. The participants representing air ambulance charities' essentially considered the results of their fund raising to be a direct expression of the public's willingness to pay. The fact that this might exceed allocated NHS funding for any given area was considered as an opportunity of self-determined resource allocation by the public. The other three stakeholder groups were, due to their background, very familiar with and generally accepting of WTP thresholds. Perhaps surprisingly, while not explicitly discussed during the qualitative research project, the general idea of WTP thresholds in healthcare seems to be an issue that the five stakeholder groups might agree on.

While the concept of a WTP threshold is not undisputed amongst health economists, ethicists and the public (Nimdet *et al.*, 2015; Cookson, 2013; Gyrd-Hansen, 2005) the degree of disagreement is probably larger when considering what the threshold should be (McHugh *et al.*, 2015; Cookson, 2013; Bobinac *et al.*, 2010).

The underlying paradigms of welfarism and extra-welfarism as well as international comparisons make for important and interesting discussions which are beyond the scope of this thesis (Schwarzer *et al.*, 2015; Gyrd-Hansen, 2005). Instead, I will focus on the context of prehospital critical care in the NHS setting, which is largely determined by guidance from the National Institute for Health and Clinical Excellence (NICE) (National Institute for Health and Clinical Excellence, 2008). NICE stresses that it *"has never identified an ICER [incremental cost-effectiveness ratio] above which interventions should not be recommended and below which they should"*, and that factors other than cost-effectiveness need to be considered in their recommendations, particularly distributive justice of limited resources (National Institute for Health and Clinical Excellence, 2008, p.18). NICE nevertheless provides a range of WTP thresholds which I summarised in Figure 9.2.

Figure 9.2 Graphic representation of levels of incremental cost-effectiveness ratios and their impact on recommendations by the National Institute for Health and Clinical Excellence, adapted from *Social Value Judgements* (National Institute for Health and Clinical Excellence, 2008)



QALY: Quality-adjusted life year, NHS: National Health Service

As Figure 9.2 shows, NICE uses two soft WTP thresholds which require decision-makers to adjust their consideration of factors other than cost-effectiveness accordingly. In regards to a WTP threshold for prehospital critical care for OHCA, all stakeholder groups argued for additional considerations for each of the fields in Figure 9.2. Commissioners expressed concern about the possibility of creating or worsening distributive injustice by allocating further resources to the prehospital treatment of OHCA. They considered ambulance services to be already very focused on OHCAs (Association of Ambulance Chief Executives, 2017) and worried about opportunity costs which might manifest as inferior care for other patient groups. Thus, the commissioners might well argue against funding of prehospital critical care for OHCA even if the ICER was less than £20,000 per QALY.

Another factor that might decrease stakeholders' WTP thresholds is the internal and external validity of the underlying research (National Institute for Health and Clinical Excellence, 2008). The prehospital researchers interviewed in this thesis would probably consider a single, observational study of prehospital critical care to be insufficient to change funding (Concato, Shah and Horwitz, 2000), unless it proved to be highly cost-effective.

In contrast, the PPI group and air ambulance charities group would likely argue for implementation of prehospital critical care for OHCA even with an ICER higher than £30,000 per QALY. The PPI group supported this argument with the principle of the Rule of Rescue (Cookson, McCabe and Tsuchiya, 2008) and resulting moral imperative to provide best possible care. While this is certainly a valid argument, NICE explicitly excluded funding considerations invoking the Rule of Rescue (National Institute for Health and Clinical Excellence, 2006).

Another consideration is that, in general, members of the public value life-extending treatments more than those improving quality of life (Nimdet *et al.*, 2015; Pennington *et al.*, 2015). The air ambulance representatives added further arguments such as indirect benefits to relatives (*"knowing that everything possible has been done")* and the public (*"knowing that help is available when required")* which are not measured in QALYs, but which people are clearly willing to pay for through donations.

The group of prehospital critical care providers also cited non-measured benefits of their practice, through support of their ALS colleagues and potentially freeing up ambulance trust resources.

Taking all these arguments into consideration, I would suggest that an ICER of up to £20,000 per QALY for prehospital critical care for OHCA could be considered cost-effective. However, for ICERs between £20,000 and £30,000 per QALY, any funding should be subject to prehospital critical care services assuring that they maximise a number of non-direct benefits, which I will further discuss in the next section.

9.4.3 Is there a future for prehospital critical care for out-of-hospital cardiac arrest?

Based on the findings of no to little clinical effectiveness of prehospital critical care and increased costs when compared to the current standard of ALS prehospital care for OHCA, funding through NHS resources cannot be recommended, or at least not without considerable limitations. However, this does not mean that prehospital critical care should not be part of an optimised care pathway, designed to increase survival following OHCA.

The first fact to consider is that the prehospital critical care services in this study only attended a subset of OHCAs, with generally better chances of survival, compared to the complete OHCA patient population. There was no evidence of better rates of survival to hospital discharge within this group (note that the propensity score matching process in Chapter 7 provided an estimate of the average treatment effect on the treated). Attempts to further expand prehospital critical care to every patient with OHCA, which was a declared goal of members of the PPI stakeholder group, are extremely unlikely to be beneficial, given the lower baseline rate of survival in this OHCA population.

On the other hand, any marginal benefit from prehospital critical care for OHCA would likely be realised in patients with ROSC, as outlined in Chapter 8. Prehospital critical care services might therefore consider restricting their dispatch criteria for OHCA with the aim of attending mainly patients with ROSC after OHCA. One possible way of achieving this would be to dispatch prehospital critical care teams only to patients with a high probability of ROSC. Factors to consider in this context would likely be the same Utstein variables which predict survival following OHCA and include the initial cardiac rhythm, witnessed OHCA, bystander CPR and age of the patient (Wibrandt *et al.*, 2015; Sasson *et al.*, 2010). As some of this information would not be available until a few minutes after arrival of the first ALS resource, this approach would introduce a trade-off between specificity for ROSC and critical care team response times. Further research would be required to identify patients with a very high or very low probability of achieving ROSC after OHCA.

Another strategy is for critical care teams not to dispatch to an OHCA at all, unless ROSC has been achieved by the attending ALS paramedics. The downside to this model is that it adds a delay from ROSC to the arrival of the critical care team, with a potential negative impact on the patient. An even more restrictive dispatch strategy would be for prehospital critical care services to only attend OHCAs if specifically requested by the attending ALS providers for either a specific intervention in OHCA due to special circumstances (see list of potential interventions in Chapter 8), neurological or cardiovascular instability preventing extrication or transfer, or if transport to an OHCA centre is indicated but cannot be achieved by the ALS provider. In general, more restrictive dispatch criteria result in longer critical care team response time and fewer activations, but possibly increased effectiveness within the population of patients with OHCA receiving prehospital critical care.

Another requirement for ongoing funding of prehospital critical care, next to attempts to optimise effectiveness through patient selection, should be a commitment to quality improvement in OHCA care. This can be achieved on a variety of levels, most of which extend beyond the individual patient with OHCA being attended by the critical care team.

The relatively large number of OHCAs attended by individual prehospital critical care providers, when compared to individual ALS paramedics, makes them an ideal target for the trial or implementation of new prehospital diagnostic or therapeutic interventions for OHCA. For example, a novel method of measuring cerebral oxygen saturations has shown promise during OHCA treatment in hospital (Nishiyama *et al.*, 2015). Testing these devices during prehospital care for OHCA in an ALS EMS system would require stocking a large number of ambulances and training a large number of paramedics, as each paramedic would be expected to only attend approximately three patients with OHCAs per year (Benger *et al.*, 2016). On the other hand, a prehospital critical care team such as PCC-1 consists of approximately 8 full-time paramedics and another 20 part-time doctors and utilises one helicopter and two rapid response vehicles. With attendance at over 300 OHCAs per year (Table 8.5, Chapter 8), trialling cerebral oxygen monitoring during OHCA could be achieved in a much more efficient manner.

As such, prehospital critical care services can and should be at the forefront of systematically testing new prehospital diagnostics and therapies for OHCA. For example, potentially beneficial interventions such as the highly invasive and resource-heavy prehospital extracorporeal membrane oxygenation (ECMO) for OHCA should not be implemented solely on the base of enthusiasm and theoretical arguments (Singer *et al.*, 2018; Hutin *et al.*, 2017). Prehospital critical care services have a responsibility to collect high quality data on non-standard interventions during OHCA and the associated effects on patients (Rehn and Kruger, 2014; Kruger *et al.*, 2011). This requires coordination and data-sharing between prehospital critical care services, ambulance services and hospitals (Perkins and Brace-McDonnell, 2015).

By being innovators and/or early adopters, prehospital critical care services can test the feasibility and usefulness of new equipment or new ways to practice (Berwick, 2003). If found to be beneficial, these can then be made available to ALS providers in the wider ambulance service, with benefit to patients not actually attended by prehospital critical care teams.

Examples of such dissemination of innovation relevant to prehospital care for OHCA can be identified in my own research. When I published my analysis of prehospital competencies in 2014, the use of end-tidal carbon dioxide monitoring during and after OHCA and the use of Adrenaline post ROSC were only available to prehospital critical care teams, not ALS paramedics (von Vopelius-Feldt and Benger, 2014a). After demonstrating that the use of both competencies is feasible and useful (at least for short term management during the prehospital phase of OHCA care), end-tidal carbon dioxide devices and the administration of Adrenaline after ROSC in hypotensive patients have become part of ALS paramedic care for OHCA (South Western Ambulance Service, 2014) . While the more complex and high-risk interventions, such as prehospital anaesthesia, will and should probably remain restricted to prehospital critical care providers (Lockey *et al.*, 2017), others, for example sedation post ROSC, could become an aspect of ALS paramedic practice in the future.

Another important role of prehospital critical care services in the innovation dissemination process, other than being innovators and early adopters, is to provide training and education for their ALS colleagues. On a system-wide level, this applies to the implementation of new interventions or new practice discussed above as well as supporting formal training and educational events.

In addition, the educator role of prehospital critical care providers is likely to be highly important in their daily interactions with ALS providers. Dyson *et al.* (2016) showed that more recent and more frequent exposure of paramedics to OHCA is associated with better outcomes after OHCA. However, in a second publication, they also demonstrated that exposure to OHCA is "*rare and declining in Victoria, Australia"* (Dyson *et al.*, 2015, p.93).

Given the lack of better survival rates with prehospital critical care team attendance in this research, prehospital critical care providers need to consider the potential impact they have beyond the individual patients that they attend. If they take over care of a patient with OHCA from their ALS paramedic colleagues, the result is a further reduction of already low exposure for ALS paramedics, with the potential for detrimental system-wide effects (Dyson *et al.*, 2016).

On the other hand, the quality of paramedics' resuscitation efforts for OHCA has been shown to drastically improve through the use of real-time feedback during and debriefing after simulated OHCA scenarios (Dine *et al.*, 2008). Initial ALS instruction during paramedics' training programmes are likely insufficient to allow them to develop into high-quality performers, unless followed by further OHCA exposure and tailored feedback (Govender *et al.*, 2016; Voss *et al.*, 2014). By assisting ALS providers in their resuscitation efforts, providing feedback and debriefing, as well as further critical care intervention if required, prehospital critical care teams can help to maximise learning from each exposure to OHCA for ALS paramedics (Public Health - Seattle & King County, 2016). By doing so, they might provide benefits that extend to all patients with OHCA, not only the fraction of OHCA patients attended by prehospital critical care services (Bobrow *et al.*, 2013).

9.4.4 Summary and limitations

There is clear potential for the improvement of prehospital care for OHCA, based on comparison with other EMS systems that achieve considerably higher survival rates. However, prehospital critical care is unlikely to be a cost-effective strategy for directly improving survival following OHCA. Stakeholders should consider their available resources, the strength of the evidence as well as potential indirect benefits of prehospital critical care in their decision-making process. Prehospital critical care services do not operate in isolation from the wider ambulance services, and there are likely to be complex interactions which can have a positive or negative impact on other providers.

Importantly, the results and discussion of this thesis apply only to the provision of prehospital critical care for adult, non-traumatic OHCA. Other OHCAs patients, such as children and those whose cardiac arrest is due to trauma, are much rarer and require different interventions. The findings of this thesis can and should not be applied to these situations.

9.5 Summary

This thesis examines prehospital critical care for OHCA from a number of different perspectives, adding a considerable amount of new knowledge to currently available evidence. The results of this thesis can be used by stakeholders to guide their decision making in regards to funding prehospital critical care for OHCA. In this process, stakeholders need to consider the degree of uncertainty inherent in any research and potential confounding and bias inherent in observational research. Further research could add value by reducing either uncertainty (through a larger sample size) or confounding (through randomised research design) but is unlikely to change the findings of no to little benefit of prehospital critical care for OHCA. Stakeholder should also include factors other than cost-effectiveness in their decision making process, such as indirect benefits from prehospital critical care, equity, budget constraints and the structure of the wider EMS system.

10. The researcher's journey

10.1 Belief, truth and justification

When I started this thesis, I had completed an analysis of prehospital critical care competencies and further examined the role of specialist paramedics in its provision (von Vopelius-Feldt and Benger, 2014a; von Vopelius-Feldt and Benger, 2014b; von Vopelius-Feldt, Wood and Benger, 2014). Having developed this detailed understanding of prehospital critical care, the next step was "*to prove that it works*", as I would phrase it during discussions with colleagues and potential supervisors. To use the terminology of the concept of the Justified True Belief (JTB, Chapter 3), I was a believer in prehospital critical care.

After starting my doctoral research fellowship, I was able to experience prehospital critical care for OHCA first hand, during my clinical shifts with PCC-1. I soon came to the conclusion that the patients we attended mainly fell into one of three categories.

The largest group were patients where, by the time the critical care team arrived, it was fairly obvious that further resuscitation was likely futile. This was often due to a combination of frailty, prolonged resuscitation and/or asystole. In these cases, the prehospital critical care providers would check that ALS had been implemented correctly and then focus on ceasing resuscitation efforts.

The second group were patients who had already achieved ROSC. We would frequently provide prehospital emergency anaesthesia or sedation and cardiovascular support, followed by transport to an OHCA centre. Most of these patients I considered to have a realistic chance of survival to hospital discharge.

Finally, the third group of patients were of younger age, in the range of 20 to 50 years. If still in cardiac arrest, the prehospital critical care providers would make use of their additional interventions, such as intravenous drugs which are not part of the ALS algorithm (see Chapter 8). Frequently, despite prolonged resuscitation efforts, the patient would be declared dead on scene. If ROSC was achieved, this was often late and in a very unstable fashion. Prehospital critical care providers worked incredibly hard to successfully transport some of these patients to hospital. However, frequently, after the patients were handed over, we acknowledged that a positive outcome was extremely unlikely.

I kept a mental log of OHCA patients I saw with the prehospital critical care team. Could I find individual patients whose life had been saved through prehospital critical care? I certainly was able to list cases where I didn't think patients would have survived to hospital admission without the critical care team. However, all of these patients I managed to follow up had died 1 or 2 days later in hospital, not unexpectedly.

I did generally have a good feeling about the second patient group whom we provided anaesthesia/sedation for. The fact that they showed signs of brain activity (therefore requiring anaesthesia/sedation) early on was a positive prognostic factor and, indeed, many of these patients survived. But would they not have survived anyway? As I learned about the counterfactual framework (see Chapter 7), I became acutely aware that, for many of the success stories of ROSC, prehospital critical care and survival following OHCA, there was a distinct possibility that the outcome would have been the same had the patient remained in the care of the ALS paramedics who provided the all-important early resuscitation in the first place.

These observations, together with increasing knowledge of the lack of evidence supporting prehospital critical care interventions, changed my perception of prehospital critical care for OHCA as well as the intent behind the research. I was now less interested in proving benefits from prehospital critical care than in finding out the truth. While I worked on my systematic review and the qualitative research, I slowly came to realise that the truth regarding benefits from prehospital critical care for OHCA depended on a number of factors, such as geography, population, the configuration of the EMS system or the perspective of the stakeholder.

Furthermore, research would only provide an estimate of the truth, with further uncertainty introduced through the observational research design. I therefore had to accept that truth was multi-faceted and unobtainable. With this ontological and epistemological shift, I decided to focus on the third aspect of the JTB, justification. Belief in prehospital critical care for OHCA was not enough and the truth unobtainable. The best I could do was to provide an estimate of truth, which could be used as justification for decision making.

10.2 Focus on methods of adjustment

With my focus on justification came an interest in research methods, particularly methods of adjustment in observational research. While I started the doctoral research fellowship by learning everything about the topic of my research, I ended it with great interest in the methods used, in particular what I refer to as the clinician-statistician interface. This was partially born out of the desire to achieve conditions which allow for causal statements regarding prehospital critical care for OHCA to be made from my own research.

Another driver was providing peer review for journals such as Resuscitation, Journal of Emergency Medicine or British Journal of Anaesthesia as well as reading publications relevant to my own topic of research. The vast majority of manuscripts that I read or reviewed described observational research designs with some form of statistical analysis beyond simple descriptive statistics. I noticed a number of issues which occurred repeatedly and which were generally caused by poor understanding of the role of statistics in clinical research. Cleophas and Zwinderman (2012, p.4) point out that, with modern computer software, " *... current statistics can include data files of many thousands of values, and can perform any exploratory analysis in less than seconds. This development, however fascinating, generally does not lead to simple results."*

The first issue, which does not arise from the clinician-statistician interface but does create many of the problems that follow, is that much of the research in prehospital or emergency care is undertaken by clinicians who believe in the intervention and want to prove that it works (von Vopelius-Feldt, 2017). While this motivation in itself is not necessarily problematic, and any clinician who undertakes research on top of their busy clinical duties should be commended, issues arise at the point of decisions being made during the analytic process. Frequently, hypotheses are tested through the statistical analysis which provides the desired outcome, rather than the most accurate one (von Vopelius-Feldt, 2018). Alternatively, multiple testing without a clear hypothesis results in many outcomes of which the desired or interesting ones can be selected.

The next temptation for researchers who are also believers is to draw conclusions which are not supported by the methods or results chosen. Of course, these observations are well known (Carmona-Bayonas *et al.*, 2017; Fernandes-Taylor *et al.*, 2011) and are part of the rationale underlying the hierarchy of evidence, with its focus on randomised controlled trials (Concato, Shah and Horwitz, 2000). However, in prehospital care and OHCA research, much of our current practice still has to rely on evidence from observational research, which will continue to be undertaken by clinicians with varying levels of statistical knowledge, supported by statisticians with little clinical knowledge of prehospital care.

I believe that, with my combined knowledge and experience of the theory and application of prehospital care and statistical methods, I can help advance evidence-based prehospital care, for patients with OHCA or other conditions. An example of the misleading consequences of a strong desire for interventions to work, incomplete understanding of statistics and inappropriate conclusion is summarised in my critique of current observational research suggesting benefits from early versus late ALS intervention (von Vopelius-Feldt, 2018).

10.3 A broader perspective

The topic of my research was very narrow – prehospital critical care is a subspecialty of emergency medicine and critical care, both of which are already small specialties within the medical community (Carr, Marvell and Collins, 2013). Within prehospital care, OHCAs account for less than 1% of all EMS resource use (Chapter 6). Despite this starting point from a very narrow focus, writing this thesis allowed me to broaden my perspective and consider issues beyond the immediate research question, yet highly relevant to the topic at hand.

In Appendix E2, I provide an ambulance service perspective on improving survival following OHCA. I demonstrate that, independently of prehospital critical care being beneficial or not, EMS systems should focus on community programmes and public access defibrillators as a priority. I also argue that community and public engagement should not stop at learning about CPR and AED use, but optimising OHCA treatment also needs to include a discussion of how we want to grow old and how we want to die. While the subject of death is rarely openly discussed in modern society, one of my palliative care colleagues pointed out that *"we only die once, so it is important that we get it right"*.

We currently subject dead or dying people to the physical assault of CPR, sometimes dragging them away from their homes and families in order to die later in an overcrowded emergency department (Timmermans, 1999). Similarly, elderly people are subjected to severe intrusions of privacy and robbed of sources of joy for the sake of medical treatments and concerns about safety (Gawande, 2014). Both Timmermans (1999) and Gawande (2014) argue for a culture change which includes realistic expectations of medical interventions and prioritising people's wishes and quality of life over desperate attempts at prolonging life. Over the course of writing this thesis, I've critically evaluated the role of prehospital critical care for OHCA but also the role our modern healthcare system plays in the wider social and cultural context, where well-intended principles can result in negative effects.

10.4 Public engagement

Interaction with the public is increasingly recognised as an important part of being a researcher (Grand *et al.*, 2015). To that degree I was fortunate that I was approached by colleagues, asking me to help with a project to teach CPR in schools, because I was *"the cardiac arrest guy".* Through writing the Introduction Chapter of this thesis, I knew that CPR and defibrillation were the only two interventions that are proven to be beneficial during OHCA, so I considered this to be an excellent opportunity to put theoretical knowledge into practice. After two initial meetings, I pointed out to the group that the project was suffering from a lack of structure and leadership, which promptly resulted in me being asked to become the chair of a newly formed steering group. Supported by the Great Western Air Ambulance Charity (GWAAC) and in cooperation with the University of the West of England, Great Western Heartstarters was officially launched in October 2016. Great Western Heartstarters provide:

- A standardised, interactive training session in first aid, CPR and public access defibrillator use, for secondary schools.
- Equipment and volunteers with nursing, paramedic or medical backgrounds to provide hands-on training.

Within the first year, the project trained over 1,000 children in CPR; for the current year we are aiming for 2,000 children. The project is successful due to hard work from all members of the steering group. My personal achievement, of which I am proud, is to have designed a presentation of a difficult subject in a way that is engaging for the children, with excellent feedback from participating schools. While the obvious target of the public engagement are the children, there are also connections being built between me as a researcher and our volunteers, between volunteers of different backgrounds, between GWAAC and UWE as well as, more recently, with the Bristol Bears Rugby Club. For me personally, the project provided a welcome contrast from the either theoretical research approach or sometimes emotionally difficult practical approach to OHCA. Figure 11.1 shows images from the Great Western Heartstarters volunteer recruitment presentation.

Figure 11.1 Slide from presentation at the volunteer induction for the Great Western Heartstarters, copyright Johannes von Vopelius-Feldt

11. Conclusions

Rates of survival following out-of-hospital cardiac arrest (OHCA) in this prospective observational research were considerably lower than those achieved by other Emergency Medical Services (EMS) internationally. Using decision analysis modelling, I demonstrated that the current standard of care, Advanced Life Support (ALS) delivered by paramedics, is cost-effective at less than £20,000 per quality-adjusted life year (QALY) gained. After propensity score matching to account for an imbalance in prognostic factors, prehospital critical care was associated with improved rates of survival to hospital arrival, when compared to ALS care. However, the primary and considerably more important outcome of survival to hospital discharge did not differ between the matched prehospital critical care and ALS care cohorts. These results were stable over a number of subgroup and sensitivity analyses. In addition, prehospital critical care is more expensive than ALS. The reasons for this lack of clinical effectiveness of prehospital critical care can be likely found in the low frequency of interventions delivered and the relatively late arrival of critical care teams at the scene of an OHCA. Stakeholders' considerations in regards to further funding of the complex intervention of prehospital critical care for OHCA will likely include additional factors, such as social acceptability, available resources and the potential for indirect benefits.

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Appendices

Appendix A1: Patient information sheet

University of the West of England BRISTOL — University Hospital Bristol NHS Foundation Trust

Version 6 - 03 August 2016

INFORMATION SHEET FOR PARTICIPANTS

REC Reference Number: 16/YH/0300

Integrated Research Application System (IRAS) ID Number: 206386

YOU WILL BE GIVEN A COPY OF THIS INFORMATION SHEET

<u>Title of study</u>

Prehospital critical care for out-of-hospital cardiac arrest

We would like to invite you to participate in a research project. Please read this information sheet carefully, and ask a member of the research team if you have any questions.

<u>What is the purpose of the study?</u>

We are currently undertaking a research project looking at the effect of prehospital critical care teams on survival following out-of-hospital cardiac arrest.

From a scientific point of view, the best way to answer this and similar questions is a randomised controlled trial, where participants are randomly allocated to receive the treatment or not. However, randomisation means that some patients will not receive the intervention studied (in this case the attendance of a critical care team). Because patients who are suffering an out-of-hospital cardiac arrest are not able to consent to participate in research, the ethical considerations make randomisation very difficult.

By discussing how different groups of people feel about randomisation, we hope to identify common issues and ways to deal with them. We hope that this will make research in prehospital care and out-of-hospital cardiac arrest of increased benefit to patients and the public, while respecting the values and concerns of individuals and society, and ensuring future research is ethical and as scientifically valuable as possible.

Why have I been invited to take part?

You have been invited to take part because the research team believes you belong to one of the groups listed below:

- ☐ Prehospital researcher
- ☐ Prehospital provider
- ☐ Member of a relevant patient and public involvement group
- ☐ Representative or stakeholder of an air ambulance charity
- ☐ Prehospital NHS lead or director, or other stakeholder

Do I have to take part?

No, participation is entirely voluntary. You can leave the study at any time without the need to give reasons.

What will happen to me if I take part?

If you choose to take part in this study, we will invite you to a focus group. These are group discussions between four to twelve people which will be led by one or more members of the research team. The research team will take notes and record the group discussion, which is estimated to last between one and two hours. We might also ask you to participate in a second round of focus groups, if required.

What are the possible benefits and risks of taking part?

Benefits: You will have a chance to inform the future of prehospital research by discussing your opinions and concerns in the focus groups.

Risks: The discussion may include the subject of death from out-of-hospital cardiac arrest. You might have some personal experience of cardiac arrest, or the loss of a person close to you. Discussing scenarios with similarities to your own experiences might trigger unpleasant memories or emotions.

Will my taking part be kept confidential?

Yes. Your participation will be known to the research team and the other participants in your focus group, but nobody else. All data will be anonymised before analysis and publication of the research results.

<u>How will information be stored and for how long?</u>

All research data will be stored on the secure University of the West of England (UWE) network drive in accordance with UWE data protection requirements, for the duration of the research. Following this, all research documents and data will be stored securely for five years, in accordance with University Hospitals Bristol NHS Foundation Trust guidelines.

<u>How is the project being funded?</u>

This research is funded by a three-year doctoral research fellowship awarded to Johannes Vopelius from the National Institute for Health Research (NIHR).

<u>What will happen to the results of the research?</u>

We will submit the results of the research for publication in a medical journal, such as the Emergency Medicine Journal. We will also present the results at national conferences. All results will be anonymised before publication or presentation.

<u>Who should I contact for further information?</u>

If you have any questions or require more information about this study, please contact Johannes using the following contact details:

Johannes von Vopelius-Feldt
johannes.vonvopelius-feldt@uwe.ac.uk
0117-3288253
Blue Lodge
Glenside Campus
University of the West of England
Blackberry Hill
Bristol BS16 1DD

<u>What if I have further questions, or if something goes wrong?</u>

If this study has harmed you in any way, or if you wish to make a complaint about the conduct of the study, you can contact the University of the West of England using the details below for further advice and information:

Professor Jonathan Benger
jonathan.benger@uwe.ac.uk
University of the West of England
Blackberry Hill
Bristol BS16 1DD

Thank you for reading this information sheet.

Appendix A2: Patient consent form

Version 4 - 03 August 2016

University of the West of England BRISTOL

University Hospital Bristol NHS Foundation Trust

CONSENT FORM FOR PARTICIPANTS IN RESEARCH STUDIES

Please complete this form after you have read the Information Sheet and/or listened to an explanation about the research.

Title of Study: Prehospital critical care for out-of-hospital cardiac arrest

REC Reference Number: 16/YH/0300

Integrated Research Application System (IRAS) ID Number: 206386

Thank you for considering taking part in this research. The person organising the research must explain the project to you before you agree to take part. If you have any questions arising from the Information Sheet or explanation already given to you, please ask the researcher before you decide whether to join in. You will be given a copy of this Consent Form to keep and refer to at any time.

	Please initial
I confirm that I understand that by initialling each box I am consenting to this element of the study. I understand that it will be assumed that if I do not initial a box it means that I DO NOT consent to that part of the study. I understand that by not giving consent for any one element I may be deemed ineligible for the study.	☐
1. I confirm that I have read and understood the information sheet dated 03 August 2016 for the above study. I have had the opportunity to consider the information and asked questions which have been answered satisfactorily.	☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason. Furthermore, I understand that I will be able to withdraw my data up to 2 weeks after my interview.	☐
3. I consent to the processing of my personal information for the purposes explained to me. I understand that such information will be handled in accordance with the terms of the UK Data Protection Act 1998.	☐

Please initial

4. **I understand that my information may be subject to review by responsible individuals from the University of the West of England for monitoring and audit purposes.** ☐

5. **I understand that confidentiality and anonymity will be maintained and it will not be possible to identify me in any publications** ☐

6. **I consent to my interview being audio recorded. I understand that the audio recordings will be transcribed by a professional transcription service.** ☐

7. **I consent to statements made during the focus group being quoted anonymously in any publications** ☐

8. **Focus group participants may share sensitive information with one another. I agree to maintain the confidentiality of the other group members.** ☐

9. **I agree to take part in this focus group** ☐

___________________	___________________	___________________
Name of Participant	**Date**	**Signature**

___________________	___________________	___________________
Name of Researcher	**Date**	**Signature**

Appendix A3: Focus group / interview guide

University of the West of England
BRISTOL

University Hospital Bristol NHS
NHS Foundation Trust

FOCUS GROUP / INTERVIEW TOPIC GUIDE (30 - 90min session)

<u>Title of study</u>

Prehospital critical care for out-of-hospital cardiac arrest

Interview objectives

- To identify aims and priorities of research in prehospital care and out-of-hospital cardiac arrest (OHCA)
- To understand the values attached to research in OHCA
- To explore how these values are balanced against individual patient rights
- To explore funding decisions in the context of limited evidence

Ground rules (5min)

- Interview / focus group is a relaxed discussion, not a question and answer session
- There are no right or wrong answers
- the aim is to fully explore all views
- The discussion is confidential – comments will not be attributed to anyone
- So please say what you really think and feel
- Support is available from the researcher or his supervisor if distress occurs either during the interview / focus group or later on (contact details on the participant information sheet)
- The interview / discussion will last 30-90min

Introductions (5-10min)

- Researcher introduction
- Summary of the PhD research project: Does prehospital critical care improve survival following OHCA, compared to advanced life support? (Adjust to stakeholder group's background)
- Participant introduction
    - Current role
    - Background

1. General attitudes towards research in prehospital care (15-20min)

- Scenario: Imagine being told about a new research study which will recruit patients in prehospital care
    - What are your priorities? Follow-up questions as needed.
    - Prompt about
        - Ethics
        - Logistics
        - Finances
        - Quality and usefulness of research
        - Reputation

2. Randomised research (15-20min)

- Review of evidence levels
    - Case series
    - Observational studies
    - Randomised controlled trials
- How do you feel about randomisation of prehospital critical care for OHCA?
    - Does this view differ from, for example, randomising a cancer drug?
    - Or a new prehospital technology?
- Do the participants' views change when considering
    - 1:1 randomisation of existing service
    - 1:n randomisation of existing service
    - 1:1 randomisation of a new service
    - Cluster randomisation of a new service

3. Funding prehospital (critical) care for OHCA (15-20min)

- In the absence of definite benefit / cost-effectiveness, how should funding decisions regarding prehospital critical care for OHCA be made?
    - Consider that not funding also equals a decision
    - What role should observational research play?

Closure (10min)

- Summary of the key points raised
- Do you want to clarify or add anything?
- Is there any other information you think would be useful to share?
- Thank you for participating

Appendix A4: Example transcript of focus group interview

Highlighted sections were used to build the themes of the framework analysis.

Name: Prehospital Critical Care Providers

Created On: 17/08/2017 10:21:01
Created By: JV
Modified On: 17/08/2017 10:21:13
Modified By: JV
Size: 24 KB

RECORDING BEGINS

JV: So it's a series of questions. It's quite a non-structured thing, so it's not like on a scale of zero to ten how much do you agree with my opinion? But giving you scenarios and see what you say and then I'll sort of follow up certain leads. It's roughly four topics and the first one is quite a general introduction question, which is supposed to be a hypothetical question but it's quite realistic. So a researcher like myself comes to you, and I say look guys, I want to do a study in cardiac arrest patients and it's gonna involve you guys. What's the sort of thing that starts going through your mind when you think about do we want to be a part of this? What are you looking for? What are you worried about? What are your hopes?

MP13: I guess your concern is that it's gonna expose that we don't bring anything to it. That you can actually **measure**. Cos I think we can all probably, you know, justify why we think we should exist. But if we don't, particularly statistically, then obviously we're potentially gonna be the authors of our own downfall. So that's the biggest concern.

MP14: I think the knowledge that it's very difficult academically to prove anything positively within research, and that there are many parties out there that will love to take a non-positive trial and portray it as a negative, which is a concern.

?: Mm.

MP15: So I think we continually have to try and prove our worth, don't we. And then if something exposes actually, guys, you're really not needed, well, like [inaudible: 1.56] nails in our own coffin.

MP16: And particularly when you say worth; financially, literally. Because of course the first three links in the chain are so simple and cheap.

MP16: And it's that last one that's the expensive bit.

[Pause]

JV: So would you look at this research and so have a look at how **good** is this actually? Are we running into danger? So how is the quality of what is being suggested?

MP13: And who. And who was trying to put it together and what was their motivation behind it. There'd be certain people, probably internally, that I think everyone would be very concerned about if they started conducting that sort of research. And people wouldn't want to take part for that reason.

JV: Any potential positives?

MP15: It's the exact opposite.
[laughter and agreement]

MP15: We can firmly stick two fingers up at people and say, right, we'll carry on doing what we're doing if not do it better.

MP16: Could also streamline what we do as well. You know, if it proves that thrombolysing people is not effective, but giving adrenaline is, then it means we can actually concentrate on doing

MP16: the really effective things all the more, all the better.

MP13: Yeah. I'm guessing it could potentially improve our task if it starts to narrow down those patients that do benefit and those patients that don't seem to. Then you could essentially get to the right patients more often than, you know, obviously their chances of survival are better and our experience at work is also improved, as it were. You know, we're going home with better outcomes for patients. More often.

MP14: Yeah, and if there's individual treatments that are exposed as causing harm, then we could remove those. And the effects on ones that potentially do give benefit.

JV: So as a group you're sort of quite looking at really the outcomes of the research, the what's gonna come out of it and how is that gonna affect your practice. I'm just gonna go through other main headlines that have come up from other groups and you can just roughly value or give your ideas about it. Do you see any reputational risk or benefit from participating in research?

MP16: On a personal professional level or a programme-wide level?

JV: As your group of professionals here.
[redacted]
MP14: With regard to the research, I think if there's any issues with the ethics, we're going to be associated with that. So there is obviously that risk that we don't need a scandal at the moment.

[laughter]

MP14: But equally if it turns out to be, you know, a seminal piece, then it would be very good to be attached to that. Quite an honour as well.

MP16: We have as a programme been saying we should be churning out more research, we should be getting involved with more research. So I think, the final results of **this** study notwithstanding, just being involved in research, particularly in an area of research so closely involved with us.

JV: How about logistics of your daily work? So things like, do I need to change my care for this research? Is it gonna get in the way of it? Is that something you'd be worried about?

MP15: It would be a worry if it did, but from what I've seen it shouldn't have any impact on service delivery. Yeah, that would be a big concern, obviously, if it was try this or focus on this.

MP16: (*Pull the?*) envelope.

[laughter]

JV: OK we'll get to the envelope a bit more in a minute.

[laughter]

JV: So the interview at some point focuses very narrowly on the randomisation, so it's good we're heading in that direction. Excellent. The other thing that's come up is finances. So research is quite expensive. And certainly groups have said well, you know, shouldn't we just spend the money on care? Rather than doing expensive research.

[short pause]

Overtalking: ?: (*Even though?*) it's expensive it's actually it's

Overtalking: MP14: That can prove that care's actually gonna be **valuable** work.

[Sounds of agreement]

MP14: Are you just putting all your money into something that's not actually gonna prove any benefit? And actually putting some money into research might prove more cost-effective.

MP15: Yeah. Presumably that care they're talking about originated from research.

MP16: Or not.

[laughter]

MP14: (*Who'd?)* argue how much you spent on adrenaline each year, and actually we don't know what [pause]
JV: Good, so going then into more the research design side. So there's different levels of evidence, and what we are operating on, what the answers, what I've identified so far, it's all observational studies. And there's always that big question mark behind there. So as I said, there's a strong push that to really answer these questions we should randomise. So, going back to your point, how would you feel if that proposal that I've got includes you at some point opening an envelope and it says yes or no to something you're doing?

[pause]

MP14: Er no. I wouldn't be comfortable with that at all.

MP15: I guess it depends what the yes and no thing is. If it's

MP13: If it's a yes or no like the LUCAS trial, whereas as I say I know are you gonna resuscitate using a LUCAS or a mechanical device, or are you just gonna do traditional manual chest compressions, I wouldn't have a massive problem with that. If it was like, are you gonna be tasked, yes or no?

MP14: [laughing] Yeah, tasked .

MP13: Well that's essentially what you need to do, to actually get the answers you want. Which you can never do. Not unless you (*hide it somewhere?*) very carefully. Then yeah, obviously that. They're two extremes. So you know, the mechanical chest device I wouldn't have any problem with that. And, you know, if it got to the extreme of being really open and I honestly wanted to find out the answers to what you were doing, is actually are we going to turn a wheel and go to this job or not, judging on what is says, yes or no in an envelope, then of course, we wouldn't feel comfortable with that.

MP16: May I just ask two questions in response to that? So, first of all, is that because it's down at an individual intervention level? Whereas if it's at the point of tasking, it's all of your interventions are being cut-off. Is that the difference?

MP13: Yes, because you hope that you can bring something to that job.

MP16: Yeah, yeah.

MP13: And if you're not allowed to go, I say you, I mean anyone delivering a different level of care.

MP16: So my next question, if that's the case, to what extent do you think what you're bringing is not interventional but is the soft skills; the leadership, the (*CRM?*), some sort of

MP13: A high proportion.

?: Mmm.

MP16?: That's exactly what I expected.

MP13: Seventy-five per cent possibly?

MP15: I assume the only way you can get close to randomising this, is to have a control group that doesn't offer a critical care response, is it? So

MP14: But then does that mean a different service where you're gonna get completely different

MP15: Well, if you're comparing ALS and then critical care to ALS only, if there's a provider that provides ALS but has no critical care facility, then I suppose you're comparing like for like, aren't you? But, it doesn't make it random? Or **does** it make it random? I don't know. It's the only way I can see that working.

MP16: You'd be able to

MP14: (*It's not for?*) prospectively.

MP15: No, it's not (-) It's only random in the fact that it's random who has a cardiac arrest on each day, isn't it. That's the random part of it.

MP16: But then you'd be able to, if you were double blinding it and placebo controlling it, you know, if we're looking at, say, thrombolysis, you could have A syringes and B syringes, half of which are filled with water.

MP14: Yeah, but that's different (-) It's very different to what (--) That is then, we're denying someone a

MP16?: (*Well?*)

MP14: intervention.

MP14: It's difficult because it's

MP16: Not of proven value.

MP14: where do you draw the line? Like [Name] said, I'd be very comfortable with LUCAS, cos we **know** that there's no evidence of (*it provides?*) benefit.

MP13: Exactly.

[laughter]

MP14: So ethically that sits very comfortably with me cos I know I'm not gonna cause any harm. In the back of my mind I know thrombolysis in cardiac arrest of a cardiac origin, is unlikely to provide significant benefit. I don't think I'd find that very uncomfortable to have an A and a B syringe. However, if it was post [inaudible: 12.31] sedation paralysis in a fighty patient,

[laughter]

MP14: yeah, I would not be happy with that.

[laughter and overtalking]

MP14?: How do you do a randomised controlled trial on that?

MP15?: Cannula has tissued, **again**.

[laughter]

MP13: But if this is just looking, this isn't looking at a specific intervention, is it, it's looking at critical care **as** an intervention.

JV: I think everybody seems to roughly agree that they're quite comfortable with randomising something like a Lucas or adrenaline, and that's what's being done across the country, iGel versus intubation. But uncomfortable with the idea of the more complex [inaudible: 14.05] interventions like yourself, like despatching yourself yes or no? And there's two possible reasons for that. One is because of what's called equipoise. Because you kind of know already that [inaudible: 14.19] chest compressions doesn't make a difference. Therefore it's easy to say well, happy to randomise that. And so is it **that** that makes the difference? Or is it, certainly from a public point of view they see a single intervention like a drug very differently to a person. So there's just something additional in there. What makes the difference for you guys? Why are you comfortable with one thing, not the other?

P15?: I think it's probably, if I quickly flashed through in my head, the ones I'd be comfortable randomising are the ones I've never particularly seen benefit from. So I've seen benefit of me being there. So I wouldn't wanna randomise me being there, but have I honestly, definitely seen the benefit of intra-arrest thrombolysis? Probably haven't seen it directly. So then I'd be happy to randomise it. So you're almost picking the interventions that you're quite happy to prove don't work. Which almost biases the

P13?: Yeah. I was gonna say, you know, even if the outcome of the arrest is that the patient is left at home because you're gonna stop. When you arrive it can look a much more sensible clinical decision to stop after you've been there for twenty minutes than before you got there. When you turn up and say, oh what've you done? Are you happy with all your Hs and Ts? And they say yes. And there's no functioning access, airway mismanaged, blah, blah, blah, blah, blah. And none of that is necessarily critical care. It's just good ALS, isn't it.

MP14: This is basically coming to our belief that we do (*well?*)

MP13: I think it's just , you could remove all the additional skills that we have, and still the task is the same and we would still, I think, have a better outcome than people that are just half

MP15: Basically we're happy to randomise things that we think don't work. Aren't we.

MP13: And we've got belief that **we** potentially do.

MP15: Yes.

MP13: Without being too arrogant.

[laughter]

MP15: Takes you back to the, you were saying about trauma centres earlier, the more you do of something, the more competent you get.

[sounds of agreement]

MP15: We're tasked to most medical cardiac arrests. So I feel I'm an expert at running a medical cardiac arrest. Whereas a normal ambulance crew probably do three to five a year,

MP14: If that, yeah. You'd do that in a shift.

JV: So that's where I'm gonna start playing devil's advocate for one, so bear with me. So it's what you've said. You've all seen the benefits of your own practice therefore you're not reaching equipoise. That place where we just don't know whether it works, because all in your minds you see benefit, so you don't reach that (*level?*) where it's unethical. So if you step outside your own system, step outside the trust, actually even step outside emergency services, if you just look at the wider healthcare system. So somewhere in the department of health I go to one of these guys and say, look, these guys are doing really good work because they see it work every time. So the person there who makes these decisions about where the funding goes, doesn't see your work. They just look at the data we've got at the moment and say, well, I don't really see a benefit. So therefore in my mind it's perfectly ethical to randomise you guys.

?: Mm.

MP13: Well I

MP13: I can see that, cos we've had it more localised, as well, recently. Where non clinical members of staff, you know, have been trying to make very difficult financial decisions, have targeted us as a potential cost saving. And on paper, you can understand why they've scrutinised it, because, you know, most of the out of hospital cardiac arrests that we go to, the patient will end up dying on the scene. You know, it won't really amount to much. So there's so much of it that you can't statistically prove in our favour. It's

MP14: Well you can statistically prove it, it's just whether it's ethical to do that, isn't it.

MP15: Yeah if you randomised us you (-) probably could.

MP13: Yeah.

MP15: Hopefully.

MP13: So we've had to prove our worth in other ways. So numbers don't help us (*face this?*).

[redacted for anonymity]

JV: Good. So going back to the funding decisions. People have different ideas of how we should come to conclusions of where to put the money. The sort of NICE academic guideline is randomised controlled trial, cost analysis, figure out how much it costs per QoLY. And that should be the only thing, the only way we do that. Now I think we all probably realise that it's extremely unlikely to happen for this sort of question. So I guess the question is what do we do alternatively. What sort of ideas about what we should feed into, so if you were making commissioning decisions, what would you base them on?

MP14: Could you, how meaningful would it be with public engagement asking what is important to the public who are essentially paying for the service? How important is the service to you? We say that we've only got this amount of money, out of ten how pissed off would you be if this got binned?

JV: So you've got public opinion in there. We try and sort of supplement that with what little research there is? Would you see a role in that sort of half-baked kind of research results? We try and incorporate them into that?

MP13: I think I've lost the question.

JV: It was basically, what's going to happen at the end of this research is I'm gonna, it's always designed to make decisions. And if there's a benefit, the reply I'm gonna get is, well, it's not a randomised trial. We're going to ignore it. But we're never gonna have a randomised controlled trial, so there's that, say, like hole in there, basically. Where decisions at the moment, because **not** funding critical care is also a decision. It's not like it's only if you decide money goes somewhere it's a decision. It's a decision one way or the other. And somehow it needs to be made. And that's what I'm trying to drive towards a bit is, is getting to an agreement. Cos everybody's like well we want this, and the others well, we can't do that. But we want this, but we can't do that. And again you're just never gonna get anywhere. Unless you say well, look, OK let's take what we realistically have and come to an agreement of how we're gonna make decisions like that.

MP13: The thing is streamlining it so that it's most effective when it is used, isn't it. So for example getting it, it's looking very internally, but we were asked to try and come up with ways that we could streamline our current system. You know a couple of bits of kit that we have available to us are never used. So we suggested getting rid of that, as were some drugs that

M13: Tenecteplase is very expensive; we're not sure how much benefit it really has. That sort of stuff was kind of explored to try and make us as lean and functional as possible.

M14: Are you more asking if this is the evidence we're going for, people'll still be able to knock it down. So how do we get around that? Some evidence is better than no evidence?

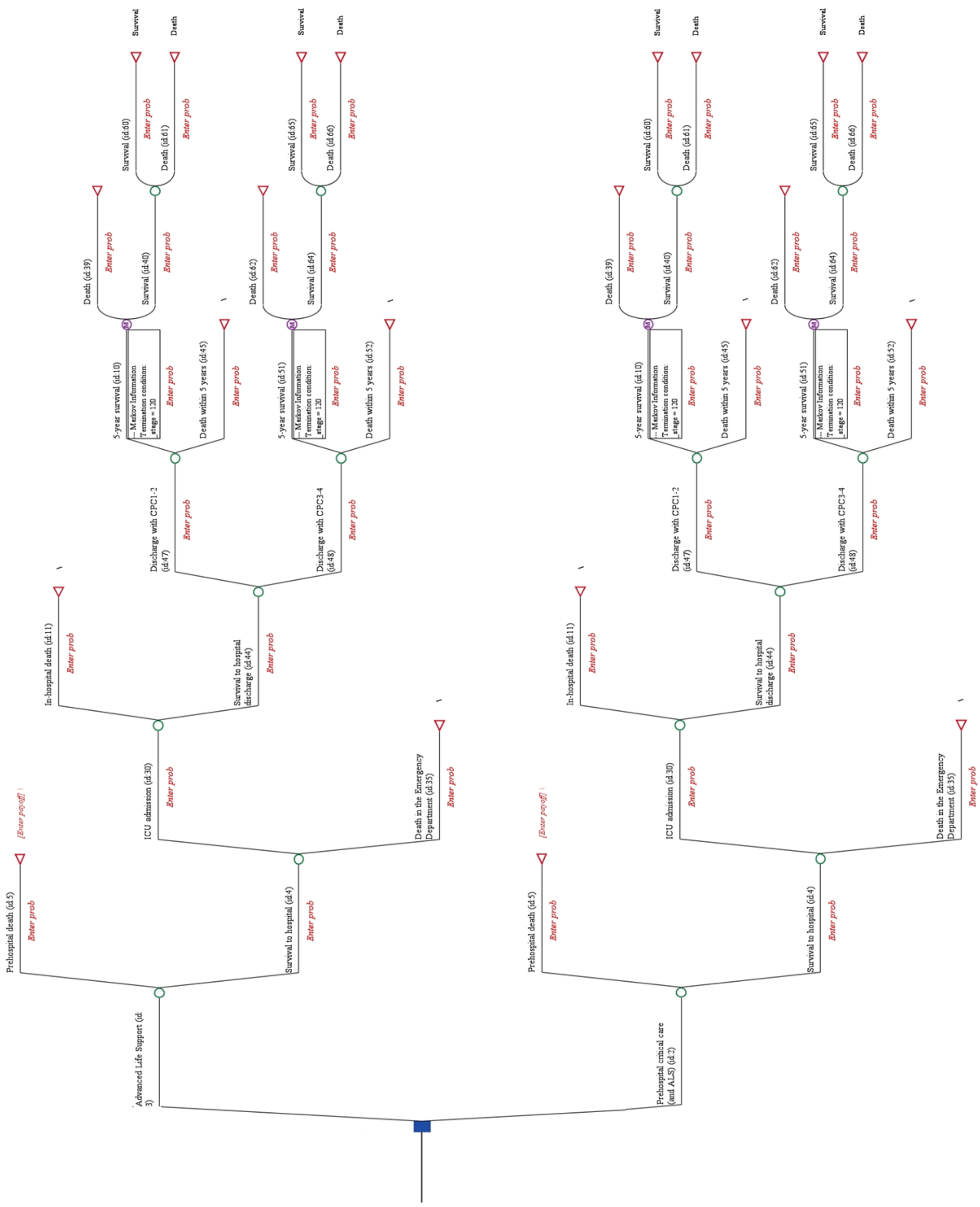
JV: Yes. [inaudible: 27.00]

MP16: To a certain extent as well, if you take the example say of sedation and paralysis post ROSC, just because it doesn't show benefit in mortality, specifically, or indeed even morbidity, doesn't necessarily mean it's not worth giving for humanitarian reasons. And then the analogy I would draw there would be the use of GCN in acute coronary syndrome. There's actually no suggestion that it improves mortality or morbidity in any way, shape or form. It's **just** given for the pain relief, and yet still (-) worth giving.

[redacted for anonymity and brevity]

[recording ends]

Appendix B1: Complete decision tree and Markov model



Appendix C1: Data sharing agreement between the University of Warwick and University Hospitals Bristol

Data Transfer Agreement

Between

University of Warwick of Coventry CV4 8UW ("University")

&

University Hospitals Bristol NHS Trust ("Hospital")

THIS AGREEMENT dated 2016 is made **BETWEEN:**

(1) **THE UNIVERSITY OF WARWICK** whose administrative offices are at Coventry CV4 8UW ("the University"); and

(2) **UNIVERSITY HOSPITALS BRISTOL NHS TRUST** whose administrative offices are at Upper Maudlin Way BS2 8HW ("the Hospital").
Each a "Party" and together the "Parties"

WHEREAS:-

(A) The University has created the collection of anonymised patient data more specifically described in Schedule 1 (collectively, the "Data"); and

(B) The Hospital requires access to the Data for the project **Prehospital critical care for out of hospital cardiac arrest: Mechanism, effect on survival, costs and the barriers to high quality research**, as described in Schedule 2 (the "Project"); and

(C) The University is willing to provide a copy of the Data to the Hospital for use in the Project subject to the following additional terms and conditions;

(D) The Hospital has in place all relevant Ethical approvals for the use of the Data and conduct of the Project as detailed in Schedule 4
NOW IT IS AGREED as follows:

1. GRANT OF LICENCE
1.1 The Data shall remain at all times the property of the University.

1.2 To the extent that the University is permitted to grant such rights, and subject to clause 3.1, the University grants to the Hospital a non-exclusive, non-transferable licence to use the Data for the sole purpose of undertaking the Project as specifically described in the Project detailed in Schedule 2 for the Term specified in Schedule 3.

1.3 In no event shall the Hospital use the Data for any commercial purposes unless agreed in writing by the University at the University's sole discretion. Such use shall be subject to a separate licence agreement.

1.4 The Hospital will not transfer the Data to any other body, or permit their use within the Hospital other than by the research group specified in Schedule 2, without (in each case) prior written consent from the University.

1.5 The Hospital will not take any steps to identify any individuals by attempting to match that data against other information.

1.6 The Data will be used only for the Project and will not be used to carry out any other studies without prior written consent from the University.

2. PAYMENT
2.1 The Data are provided free of charge.

3. WARRANTIES AND INDEMNITIES

3.1 The Hospital understands that the University makes no representations and gives no warranties of any kind in relation to the Data. In particular, no warranties are given about quality or fitness for a particular purpose; or that the use of the Data by the Hospital will not infringe any intellectual property or other rights; or that the Data do not contain any defamatory material.

3.2 The University will not be liable for any use made of the Data by the Hospital including without limitation publication under clause 4.7.

3.3 Subject to clause 8, the Hospital agrees to indemnify the University against all and any direct losses (including without limitation direct or consequential damages or losses), costs, fees, claims, demands and liabilities which may arise out of the Hospital's use of the Data

4. CONFIDENTIALITY AND PUBLICATION PROCEDURES

4.1 For the purpose of this clause, "Confidential Information" means all and any specifications, drawings, circuit diagrams, tapes, discs and other computer-readable media, documents, information, techniques and know-how, including but not limited to the Data, which are disclosed by one Party to the other in connection with the Project and Project and marked or labelled "Proprietary", "Confidential" or "Sensitive" by the disclosing party at the time of disclosure; or are written, prepared or generated in the course of, and as part of, the Project and Project.

4.2 Subject to clauses 4.3 and 4.5, each party will use its reasonable endeavours not to disclose to any third party any Confidential Information received from the other party.

4.3 Clause 4.2 will not apply to any Confidential Information which:

4.3.1 is known to the receiving party before disclosure, and not subject to any obligation of confidentiality owed to the disclosing party; or

4.3.2 is or becomes publicly known without the fault of the receiving party; or

4.3.3 is obtained by the receiving party from a third party in circumstances where the receiving party has no reason to believe that there has been a breach of an obligation of confidentiality owed to the disclosing party; or

4.3.4 the receiving party can establish by reasonable proof was substantially and independently developed by officers or employees of the receiving party who had no knowledge of the disclosing party's Confidential Information; or

4.3.5 is approved for release in writing by an authorised representative of the disclosing party; or

4.3.6 the receiving party is required to disclose by law or regulation (provided that, in the case of the Freedom of Information Act 2000, none of the exceptions to that Act applies to the information disclosed) or by order of a competent authority (including any regulatory or governmental body or securities exchange); provided that, where practicable, the disclosing party is given reasonable advance notice of the intended disclosure and provided that the relaxation of the obligation of confidentiality shall only last for as long as necessary to comply with the relevant law, regulation or order and shall apply solely for the purposes of such compliance.

4.4 If either party to this Agreement receives a request under the Freedom of Information Act 2000 to disclose any information that, under this Agreement, is Confidential

Information, it will notify and consult with the other party. The other party will respond within 5 days after receiving notice if that notice requests the other party to provide information to assist in determining whether or not an exemption to the Freedom of Information Act 2000 applies to the information requested under that Act.

4.5 Subject to clause 4.7 below, each party's duty to protect Confidential Information received under this Agreement shall survive the termination of the Project and the Project and continue in full force without limit in point of time the Hospital acknowledges that the Data may contain some details that constitute personal information and shall ensure that such information is not disclosed and treated in accordance with the Data Protection Act 1998.

4.6 Where the Hospital wishes to submit for publication results of the Project in which the University has provided the Data pursuant to this Agreement, the Hospital will use all reasonable endeavours to submit a copy of the proposed publication to the University for review not less than thirty (30) days in advance of the submission for publication. The University may require the Hospital to delay submission for publication if in the University's opinion such delay is necessary in order to protect the University's legitimate interests (including those of any relevant funder). The Hospital agrees to take into consideration any reasonable comments made by the University regarding the proposed publication with respect to the Data and shall not unreasonably refuse to include amendments requested by the University where these relate to the Data. The University shall notify the Hospital in writing with its comments regarding the proposed publication within thirty (30) days after the receipt of the publication by the University, failing which the Hospital shall be free to assume that the University has no objection to the proposed publication.

4.7 The Hospital agrees to acknowledge Warwick Clinical Trials Unit at the University of Warwick as the source of the Data and shall make additional acknowledgements as the University requests from time to time.

5. INTELLECTUAL PROPERTY RIGHTS

5.1 This Agreement does not affect the ownership of any Intellectual Property in the Data and the Intellectual Property in them will remain the property of the University. No licence to use any Intellectual Property is granted or implied by this Agreement except the rights expressly granted in this Agreement.

5.2 Nothing in this agreement shall restrict the University's right to licence the Data to other commercial and non-commercial entities.

6. ASSIGNMENT

6.1 This Agreement is not transferable, nor any of the rights granted in it, and neither party may purport to assign it (in whole or in part) without the prior written consent of the other.

7. TERM AND TERMINATION

7.1 This Agreement shall have effect for the Term stated in Schedule 3 unless terminated earlier in accordance with clause 7.2.

7.2 The Parties may terminate this Agreement with immediate effect by giving written notice to the other Party if:

(a) The University commits a material breach of this Agreement.

(b) The Hospital commits a material breach of this Agreement.
7.3 Upon the expiration or termination of this Agreement, howsoever caused, or at the written request of the University, the Hospital and any party who may have received Data under clause 1.4 shall immediately cease all use of the Data received pursuant to this Agreement; and within eight (8) days thereafter shall destroy or return to the University all copies of Data and related information in its possession, sending written confirmation of despatch or destruction to the University.

8. LIMITATION OF LIABILITY
8.1 The University makes no representation or warranty that advice or information given by its employees, students, agents or appointees, or the content or use by the Hospital of any materials, works or information provided in connection with the Data, will not constitute or result in infringement of third-party rights

8.2 The University accepts no responsibility for any use which may be made by the Hospital of the Data or of the results of the Project generated by the Hospital, nor for any reliance which may be placed on the Data by the Hospital, nor for advice or information given to the Hospital in connection with them.

8.3 The Hospital undertakes to make no claim in connection with this Agreement or its subject matter against any employee, student, agent or appointee of the University (apart from claims based on fraud or wilful misconduct). This undertaking is intended to give protection to individual researchers: it does not prejudice any right which the Hospital might have to claim against the University. The benefit conferred by this sub-clause is intended to be enforceable by the persons referred to in it.

8.4 Subject to clause 8.5, the liability of either party to the other for any breach of this Agreement, for any negligence, or arising in any other way out of the subject-matter of this Agreement, the Project or the results will not extend to any indirect damages or losses, or to any loss of profits, loss of revenue, loss of business, loss of data, loss of contracts or opportunity, whether direct or indirect, even if, in any such case, the party bringing the claim has advised the other of the possibility of those losses or if they were within the other party's contemplation.

8.5 Nothing in this Agreement limits or excludes either party's liability for:
8.5.1 death or personal injury resulting from negligence; or

8.5.2 any fraud or for any sort of other liability which, by law, cannot be limited or excluded.
8.6 If any sub-clause of this clause 8 is held to be invalid or unenforceable under any applicable statute or rule of law then it shall be deemed to be omitted, and if as a result any party becomes liable for loss or damage which would otherwise have been excluded then such liability shall be subject to the remaining sub-clauses of this clause 8.

8.7 In any event, the maximum liability of any Party under or otherwise in connection with this Collaboration Agreement or its subject matter shall not exceed £100,000.

9. GENERAL
9.1 This Agreement shall be governed by English Law, and the parties submit to the exclusive jurisdiction of the English Courts for the resolution of any dispute which may arise out of this Agreement.

9.2 Clause headings are inserted in this Agreement for convenience only, and they shall not be taken into account in the interpretation of this agreement.

9.3 Nothing in this Agreement shall create, imply or evidence any partnership or joint venture between the University and the Hospital or the relationship between them of principal and agent.

9.4 This Agreement constitutes the entire agreement between the parties with regard to the subject matter.

9.5 Any variation of this Agreement shall be in writing and signed by authorised representatives for both parties.

9.6 The Parties shall not assign, subcontract or transfer any rights, duties or obligations under this agreement without the prior written approval of the other Party.

SCHEDULES
1. Description of the Data
2. The Project
3. Term
4. Ethical Approval

AS WITNESS the hands of authorised signatories for the parties on the date first mentioned above.

SIGNED for and on behalf of **UNIVERSITY HOSPITALS BRISTOL NHS TRUST**
Name: **Johannes von Vopelius-Feldt**
Position: **Research Fellow, University Hospitals Bristol NHS Foundation Trust**
Signature:
Date: **24/09/2016**

SIGNED for and on behalf of **THE UNIVERSITY OF WARWICK:**
Name: **Dr Navdeep Bains**
Position: **Head of Research Support, Funding and Contracts**
Signature:
Date: **24/09/2016**

Schedule 1

The Data Collection Title	**Details of Data to be shared by the University**
Out of Hospital Cardiac Arrest Outcomes project (OHCAO)	1. Ambulance incident case number 2. Patients age 3. Age unit 4. Patients sex 5. Date of EMS call 6. Time of EMS call 7. Location of EMS occurrence 8. Occurrence witnessed by 9. Bystander commenced CPR 10. Public access defibrillator used by the public 11. Was a ROSC noted on arrival of EMS staff 12. Initial aetiology of cardiac arrest 13. Initial cardiac arrest rhythm 14. Do not attempt resuscitation order in place 15. EMS chest compressions 16. ROSC at hospital handover 17. Death confirmed by EMS 18. Receiving hospital code / name 19. Survival to discharge 20. Time EMS vehicle stops 21. Time of ROSC

Schedule 2

The Project

Chief Investigator and Name of Hospital's Research Group

Dr Johannes Von Vopelius-Feldt, NIHR Doctoral Research Fellow
Academic Department for Emergency Care
University Hospitals Bristol NHS Foundation Trust
Upper Maudlin Street
BS2 8HW Bristol
johannes.vonvopelius-feldt@uwe.ac.uk

The Project
Prehospital critical care for out-of-hospital cardiac arrest

Introduction
Survival rates from out-of-hospital cardiac arrest (OHCA) remain low, despite remarkable efforts at improving care. A number of ambulance services in the United Kingdom (UK) have developed prehospital critical care teams (CCTs) which attend critically ill patients, including OHCA. However, current scientific evidence describing CCTs attending OHCA is sparse and research to date has not demonstrated clear benefits from this model of care.

Methods and analysis
This prospective, observational study will describe the effect of CCTs on survival from OHCA, when compared to advanced-life-support (ALS), the current standard of prehospital care in the UK. In addition, we will describe the association between individual critical care interventions and survival, and also the costs of CCTs for OHCA.
To examine the effect of CCTs on survival from OHCA, we will use routine Utstein variable data already collected in a number of UK ambulance trusts. We will use propensity score matching to adjust for imbalances between the CCT and ALS groups. The primary outcome will be survival to hospital discharge, and the secondary outcome survival to hospital admission.
We will record the critical care interventions delivered during CCT attendance at OHCA. We will describe frequencies and use multiple logistic regression to examine possible associations with survival.
Finally, we will undertake a cost analysis of CCTs for OHCA. This will follow a previously published EMS cost analysis toolkit and will take into account the costs incurred from the use of a helicopter and costs currently covered by charities.

The Project does not extend to:

- the Hospital commercially exploiting the Data;
- nor to the evaluation or any other use of the Data by the Hospital outside the Project described above.

Schedule 3

Term
This Agreement shall take effect on the date of the signature of the last party to sign this agreement, and shall terminate on 31/12/2018 (the "Term").

Schedule 4

Ethical approval (reference 16/YH/0300)

Appendix C2: Optimisation of propensity score matching

In Chapter 7, Figure 7.3 I described a stepwise approach to propensity score matching. In this process, a logistic regression model predicting the propensity score is optimised first. In a separate step, the matching strategy is optimised. However, in the actual data used in Chapter 7, the matching strategy interacted with the performance of the propensity score prediction model in unpredictable ways. I therefore used a matrix approach, which combined a number propensity score prediction models with a number of matching strategies.

C2.1 Examination of predictors of intervention and outcome

The first step in the process of optimising the logistic regression model for predicting the propensity score was to understand which factors predict the intervention of prehospital critical care and/or the outcome of survival to hospital discharge after OHCA. Table C2.1 shows the results of a basic multiple logistic regression model (without any interaction terms) which examines associations between all Utstein variables available for analysis in Chapter 7, and the attendance of a prehospital critical care team or survival to hospital discharge.

Table C2.1 Odds ratios and 95% confidence intervals of factors potentially predicting prehospital critical care attendance or survival to hospital discharge

	Prehospital critical care attendance	**Survival to hospital discharge**
Age (per year increase)	0.97 (0.97 – 0.98)*	0.96 (0.96 – 0.97)*
Gender	0.99 (0.82 – 1.20)	1.02 (0.78 – 1.34)
Location of OHCA		
Private residence	1 (reference)	1 (reference)
Public area	1.27 (1.02 – 1.59)*	1.59 (1.19 – 2.12)*
Assisted living	0.52 (0.28 – 0.95)*	0.18 (0.02 – 1.32)
Other	0.69 (0.41 – 1.15)	1.98 (1.32 – 2.98)*
Aetiology		
Presumed cardiac	1 (reference)	1 (reference)
Drug overdose	1.01 (0.58 – 1.77)	4.66 (2.19 – 9.92)*
Event witnessed		
Unwitnessed	1 (reference)	1 (reference)
Witnessed	1.34 (1.10 – 1.65)*	1.96 (1.37 – 2.81)*
Witnessed by EMS	0.82 (0.56 – 1.21)	4.57 (2.90 – 7.20)*
Cardiac rhythm		
Asystole	1 (reference)	1 (reference)
PEA	1.06 (0.83 – 1.36)	3.73 (2.24 – 6.21)*
VF / pulseless VT	1.67 (1.36 – 2.06)*	35.65 (22.83 – 55.67)*
Bystander CPR	1.21 (0.98 – 1.51)	0.90 (0.65 – 1.24)
AED use	1.03 (0.62 – 1.70)	0.85 (0.43 – 1.67)
EMS response time		
< 10min	1 (reference)	1 (reference)
10 – 20min	1.84 (1.50 – 2.25)*	0.40 (0.27 – 0.59)*
>20min	2.00 (1.42 – 2.82)*	1.02 (0.56 – 1.86)
Time of 999 call		
7am – 7pm	1 (reference)	1 (reference)
7pm – 1am	0.60 (0.48 – 0.74)*	1.01 (0.76 – 1.34)
1am – 7am	0.08 (0.05 – 0.14)*	0.90 (0.63 – 1.30)

** Statistically significant result*

Due to this being a crude model, individual parameters in Table C2.1 should be interpreted with caution.

The multiple logistic regression identifies a number of variables associated with prehospital critical care attendance and survival (patient's age, Utstein location of OHCA, witnessed event, cardiac rhythm and EMS response time). Other variables were associated only with critical care team attendance but not survival following OHCA (time of 999 call) or vice versa (aetiology of OHCA). Note that neither bystander AED use nor bystander CPR were associated with prehospital critical care or survival. In the case of AED use, this is likely due to the small numbers (n=116). Bystander CPR on the other hand has been proven to improve survival. This effect is likely through prolongation of shockable rhythm until EMS arrival and in this model without any interactions, the effect is likely absorbed in that of the cardiac rhythm.

After analysing the associations between the variables listed in Table C2.1 and prehospital care attendance and/or survival to hospital discharge, I identified the variables of gender, time of 999 call and AED use as potentially ignorable. All other variables were considered to be clinically and/or statistically important predictors of survival, and excluding them from the model was very unlikely to result in good balance of covariates after propensity score matching.

C2.2 Combining propensity score prediction models and matching strategies

Table C2.2 shows the results of bias reduction achieved by different methods of propensity score prediction, followed by different matching strategies with calliper of 0.2*the standard deviation of the propensity score. The initial, full model included the following variables: Witnessed event, patient gender, time of 999 call, age, Utstein location, bystander CPR, EMS response time, aetiology of OHCA, first recorded cardiac rhythm, and bystander AED use. The order in which variables were excluded from the model was determined by existing evidence about variables and the results of the multiple logistic regression analysis in Table C2.1.

Table C2.2 Combination of stepwise-backwards selection of variables in multiple logistic regression model and different matching strategies to predict propensity score of prehospital critical care attendance at out-of-hospital cardiac arrest

	Matching strategy				
Propensity score prediction model	**1:1 ***	**1:2***	**1:3***	**1:4***	**Mahalanobis**
1. Full model					
Rhythm	1.5%	8.6%	**7.1%**	10.8%	16.8%
Witnessed	4.1%	9.5%	**5.8%**	9.2%	8.5%
Aetiology	0.0%	3.3%	**3.0%**	4.4%	2.1%
2. Drop gender					
Rhythm	2.6%	3.1%	**5.7%**	12.1%	16.1%
Witnessed	2.2%	5.5%	**5.0%**	8.7%	9.8%
Aetiology	7.0%	6.4%	**1.6%**	3.5%	2.8%
3. Drop time of 999 call					
Rhythm	2.9%	3.4%	**5.8%**	10.6%	16.7%
Witnessed	1.9%	3.2%	**7.2%**	10.9%	12.6%
Aetiology	2.8%	5.2%	**3.8%**	2.1%	4.3%
4. Drop AED use					
Rhythm	3.1%	3.9%	**4.5%**	10%	17.9%
Witnessed	2.3%	8.0%	**5.7%**	7.0%	9.3%
Aetiology	1.8%	2.4%	**2.3%**	4.1%	3.0%
5. Drop gender					
Drop time of 999 call					
Rhythm	1.7%	4.0%	**7.1%**	9.9%	18.3%
Witnessed	1.7%	2.5%	**4.1%**	10.1%	17.1%
Aetiology	4.9%	4.0%	**2.4%**	2.6%	8.3%
6.Drop AED use					
Drop time of 999 call					
Rhythm	5.3%	1.7%	**5.1%**	11.0%	18.2%
Witnessed	5.8%	4.1%	**6.9%**	10.2%	13.8%
Aetiology	2.8%	3.7%	**2.5%**	1.5%	5.1%
7. Drop AED use					
Drop gender					
Rhythm	2.5%	3.4%	**5.2%**	11.6%	16.7%
Witnessed	7.2%	7.0%	**5.4%**	6.2%	10.5%
Aetiology	4.9%	5.3%	**1.7%**	3.5%	4.0%
8. Drop AED use					
Drop gender					
Drop time of 999 call					
Rhythm	1.0%	3.3%	**6.2%**	9.9%	20%
Witnessed	2.9%	1.0%	**4.2%**	9.6%	18.7%
Aetiology	7.0%	3.2%	**2.8%**	3.2%	9.4%

** For practical reasons, all trials utilised matching with calliper of 0.02 and no replacement*

Of the MLR models and matching strategies in Table C2.2, 1:3 matching reliably resulted in the optimal trade-off between covariate balance and power. Mahalabonis matching resulted in higher power, as it matches all available cases, but consistently poor covariate balance. I therefore chose models 4, 6 and 7 with 1:3 matching for a final comparison.

In this final selection step, I examined the balance of all covariates, using a combination of standardised difference and clinical weighting of importance of each variable. The model which achieved optimal balance across all covariates and was therefore selected for analysis in Chapter 7 was model 6, which excludes AED use and time of 999 call.

Appendix C3: Stata SE code for 1:3 propensity score matching, without replacement

I used Stata SE (version 14, StataCorp) to undertake 1:3 propensity score matching, without replacement. Unfortunately, the plugin used most commonly for propensity score matching in Stata SE, *psmatch2,* only performs 1:n matching with replacement. I therefore had to create a workaround solution to achieve the desired matching strategy. The code in Box C3.1 is an example of the programming I performed, which includes the following steps

1. Reduction of the dataset to complete cases only
2. Propensity score prediction, using multiple logistic regression with the variables specified in Chapter 7
3. Matching of each case of out-of-hospital cardiac arrest (OHCA) with prehospital critical care attendance to up to three cases with Advanced Life Support, with replacement. This required further steps
    a. Running *psmatch2* 1:1 matching three times
    b. After each 1:1 match, record the matched pairs and exclude matched prehospital critical care cases from further analysis
    c. Recreate an output that mirrors the original *psmatch2* output and which can be used for further analysis

Box C3.1 Stata SE do-file for 1:3 propensity score matching, without replacement; each line preceded by one or more stars is not part of the active code but an annotation (Page 1 of 4)

```
                    ***** complete case analysis *****

  *** 1:3 matching without replacement, using repeated 1:1 matching with
                              psmatch2 ***

*** step 1: reduce to complete cases only (==. means missing data)
drop if survival==.
drop if witnessed==.
drop if agecat==.
drop if gender==.
drop if utstein_cat==.
drop if bystander_cpr==.
drop if response_time==.
drop if aetiology==.
drop if rhythm==.
drop if aed_use==.
drop if rosc_hospital==.
```

Box C3.1 ... continued (page 2 of 4)

```
*** step 2: predict the propensity score (pscore)

logistic cct_arrived i.witnessed i.gender i.agecat i.utstein_cat///
i.bystander_cpr i.response_timecat i.aetiology i.rhythm

predict pscore
sum pscore


*** step 3: one-to-three matching on the propensity score, without
replacement

** prepare dataset

* create copy of propensity score
gen pscore_original=pscore

* random order
set seed 1000
gen x=uniform()
sort x


** Round 1

* nearest neighbour 1:1 matching with caliper 0.20*SD
psmatch2 cct_arrived, pscore(pscore) caliper (0.018) noreplacement
descending

* remove matched controls by changing propensity score to 91
replace pscore=91 if cct_arrived==0 & _weight==1

* keep ID of matched control by generating new _n1 variable
gen n1=_n1
gen id=_id

* generate paired ID for later analysis
gen pair = _id if pscore==91
replace pair = _n1 if _treated==1
bysort pair: egen paircount = count(pair)
replace pair=. if paircount!=2
drop paircount


** Round 2

* nearest neighbour 1:1 matching with caliper 0.20*SD
sort x
psmatch2 cct_arrived, pscore(pscore) caliper (0.018) noreplacement
descending
```

Box C3.1 ... continued (page 3 of 4)

```
* remove matched controls by changing propensity score to 92
replace pscore=92 if cct_arrived==0 & _weight==1

* keep ID of matched control by generating new _n2 variable
gen _n2=_n1

* generate paired ID for later analysis
gen pair2 = _id if pscore==92
replace pair2 = _n2 if _treated==1
gsort pair2 _treated
replace pair=pair[_n+1] if pair==. & pair2!=.
bysort pair: egen paircount = count(pair)
drop pair2 paircount

** Round 3

* nearest neighbour 1:1 matching with caliper 0.20*logit of SD
sort x
psmatch2 cct_arrived, pscore(pscore) caliper (0.018) noreplacement
descending

* remove matched controls by changing propensity score to 93
replace pscore=93 if cct_arrived==0 & _weight==1

* keep ID of matched control by generating new _n3 variable
gen _n3=_n1

* generate paired ID for later analysis
gen pair2 = _id if pscore==93
replace pair2 = _n3 if _treated==1
gsort pair2 _treated
replace pair=pair[_n+1] if pair==. & pair2!=.
bysort pair: egen paircount = count(pair)
drop pair2


** tidy up and recreate psmatch2 output

*create 1:3 match descriptor for all matched
gen one_to_n=(paircount-1)
replace one_to_n=. if one_to_n==-1
drop paircount
sort _treated
by _treated: tab one_to_n

* reconstruct matches to original ID numbers
gsort pair pscore
replace _n2=id[_n+2] if pscore[_n+2]==92 & _n2!=.
replace _n3=id[_n+3] if pscore[_n+3]==93 & _n3!=.
drop _n1
rename n1 _n1
```

Box C3.1 ... continued (page 4 of 4)

```
* recreate output from 1:n matching with psmatch2
replace _id=id
replace _weight=1 if cct_arrived==1 & _n1!=.
replace _weight=1 if cct_arrived==0 & one_to_n==1
replace _weight=0.5 if cct_arrived==0 & one_to_n==2
replace _weight=0.333 if cct_arrived==0 & one_to_n==3
replace _nn=0 if cct_arrived==0
replace _nn=0 if cct_arrived==1 & _n1==.
replace _nn=1 if cct_arrived==1 & _n1!=. & _n2==.
replace _nn=2 if cct_arrived==1 & _n1!=. & _n2!=. & _n3==.
replace _nn=3 if cct_arrived==1 & _n1!=. & _n2!=. & _n3!=.
replace _support=1 if _treated==1 & _weight==1
replace _pscore=pscore_original
order _pscore _treated _support _weight _id _n1 _n2 _n3 _nn , after (x)
sort pair

* check if this worked by describing n-matches
tab _nn if cct_arrived==1
```

Appendix D1: Paper data collection form used for PCC-2 (anonymised)

Critical care teams and OHCA - Data collection form

Date:

Crew (ID or names)
1.
2.
3.

Incident number:
Dispatch: HEMS desk / crew request
Response type: Helicopter / RRV
Stood down / arrived at patient
At scene time:
ROSC prior to arrival: Yes / No

Interventions in cardiac arrest

- ☐ IO access
- ☐ Surgical airway
- ☐ Atropine IV
- ☐ Calcium IV
- ☐ Thrombolysis
- ☐ Mechanical CPR
- ☐ ROLE outside JRCALC guidance
- ☐ Central access
- ☐ Ultrasound (any application)
- ☐ Magnesium IV
- ☐ Sodium Bicarbonate IV
- ☐ Thoracostomy
- ☐ Peri-mortem c-section
- ☐ **None of the above**
- ☐ **Other**____

Interventions after ROSC

☐ **Sustained ROSC achieved (>5min)**

- ☐ Rapid sequence induction
- ☐ Central access
- ☐ Amiodarone IV
- ☐ Calcium IV
- ☐ Atropine IV
- ☐ Thrombolysis
- ☐ ROLE outside JRCALC guidance
- ☐ Any sedation and/or paralysis
- ☐ Any vasopressor IV
- ☐ Magnesium IV
- ☐ Sodium Bicarbonate IV
- ☐ Thoracostomy
- ☐ DC cardioversion
- ☐ **None of the above**
- ☐ **Other**____

Transport

- ☐ Air transfer
- ☐ Ground transfer
- ☐ Bypass of nearest hospital for cardiac centre
- ☐ Left at scene (death)

Treatment decisions

- ☐ One or more critical care intervention(s) that would usually be given were withheld on the basis of futility (in the patient's best interests)

Version 4 11/10/2016 Contact [redacted] if any questions

Appendix D2: The potential effects of further data from ambulance trusts

As discussed in Chapter 7, at the time of writing this thesis, not all potential data from ambulance trusts had been transferred to me for analysis. In addition to the data used for the analysis in Chapter 7, I currently have critical care team data from 90 and 682 cases of out-of-hospital cardiac arrest (OHCA) from two further prehospital critical care service (PCCs), PCC-7 and PCC-8, respectively. I am expecting a further 100 OHCA cases from PCC-7 and I am awaiting the Out-of-Hospital Cardiac Arrest Outcomes (OHCAO) Registry data from the corresponding ambulance trusts, Trust Charlie and Trust Delta. Once this data is available, I will repeat the analyses presented in Chapter 7, with a larger dataset.

D2.1 Statistical effect of increasing sample size

The further data from Trust Charlie and Trust Delta will potentially increase the sample size by 50-100%. It is possible that the current results could be overturned by the later analysis, however, this is unlikely. The key question is: what would the likely effect of a bigger sample size be? The current analyses have the power to detect an approximately 4-5% absolute difference in survival with an alpha of 0.8. However, the estimated average treatment effect on the treated (ATT) is 0%, as demonstrated in Chapter 7, Table 7.8. If the sample size were to be doubled, the additional cases would need to contain at least a 6% difference in ATT, in order to reach the new threshold of 3% absolute difference in treatment, which would be detectable with the new sample size with an alpha of 0.8. With the adjusted odds ratios of the primary and secondary analyses sitting very closely to, and on either side of 1.0 (Chapter 7, Figure 7.8), the possibility of the treatment effect in the additional data being 6% or larger is very low.

D2.2 Comparing prehospital critical care services

The question, which this appendix is trying to answer is whether it is likely that the effectiveness of PCC-7 or PCC-8 might be different from the prehospital critical care services already included in the analysis. I will attempt to predict the likelihood of this by comparing PCC-7 or PCC-8 to the already included prehospital critical care services. Tables D2.1 and D2.2 compare key features and the frequency of prehospital critical care interventions between PCC-7 and PCC-8, and the prehospital critical care services which are already included in the analysis.

Table D2.2 Overview of key features of PCC-7 and PCC-8, compared to prehospital critical care services already included in the primary analysis

	PCC-7	**PCC-8**	**PCCs in Chapter 7**
Activations	Not available	682	**969**
Treated	90 (-)	674 (99%)	**866 (89%)**
Treated per month	15	112	**10 (mean)**
Helicopter use	0 (0%)	0 (0%)	**563/796 (71%)**
Response time	Not available	18min	**28min**
Physician presence	0 (0%)	0 (0%)	**540/796 (68%)**

PCC: Prehospital critical care service

Table D2.2 Prehospital critical interventions delivered during OHCA and after return of spontaneous circulation (ROSC), stratified by patient outcomes

Interventions during OHCA			
	PCC-7 (n=77)	**PCC-8 (n=584)**	**PCCs in Chapter 7 (n=520)**
Ultrasound	45 (58%)	117 (20%)	**97 (19%)**
IV Magnesium	1 (1%)	0 (0%)	**31 (6%)**
IV Calcium Chloride	0 (0%)	10 (2%)	**15 (3%)**
IV Sodium Bicarbonate	0 (0%)	0 (0%)	**27 (5%)**
Thoracostomy	0 (0%)	18 (3%)	**5 (1%)**
ROLE outside of JRCALC	8 (10%)	56 (10%)	**124 (24%)**
Mechanical CPR	49 (91%)	40 (7%)	**204 (39%)**
Sedation and/or paralysis	0 (0%)	2 (0%)	**11 (2%)**
Thrombolysis	0 (0%)	16 (3%)	**3 (1%)**
Interventions after ROSC			
	PCC-7 (n=33)	**PCC-8 (n=243)**	**PCCs in Chapter 7 (n=299)**
Rapid sequence induction of anaesthesia (RSI)	1 (3%)*	30 (13%)*	**94 (31%)**
Sedation and/or paralysis (excluding RSI)	4 (12%)	70 (29%)	**64 (21%)**
IV inotropes or vasopressors	11 (33%)	71 (30%)	**94 (31%)**
IV amiodarone	0 (0%)	5 (2%)	**9 (3%)**
IV magnesium	0 (0%)	2 (1%)	**7 (2%)**
IV sodium bicarbonate	0 (0%)	0 (0%)	**5 (2%)**
DC cardioversion	2 (6%)	10 (4%)	**5 (2%)**
Ultrasound	7 (21%)	3 (1%)	**13 (4%)**
Bypass of nearest hospital for OHCA centre	(Data not available)	(Data not available)	**65 (22%)**

** Supported by regional air ambulances with prehospital physicians on board*
PCC: Prehospital critical care service

The configuration of PCC-7 is very similar to that of PCC-1 and PCC-5 (if responding by rapid response vehicle) – one or more prehospital critical care providers respond from a central, urban location to OHCA within a reasonable radius. The only difference is that PCC-7 provides a purely paramedic-delivered service of prehospital critical care, which should not affect outcomes significantly.

With the exception of ultrasound and mechanical CPR, no prehospital critical care intervention is undertaken more frequently by PCC-7 when compared to the current services (Table D2.2). The configuration of PCC-8 is an outlier amongst the critical care services. PCC-8 is the only service which does not respond from a central location but has multiple critical care paramedics stationed across the region, working in parallel. This explains the higher number of patients with OHCAs treated per month (note that the PCC-8 critical care team will also be much larger than the other prehospital critical care teams) and the shorter median response time (Table D2.1). While the shorter response time might be beneficial, the frequency of most interventions is comparable to those of the current critical care services (Table D2.2).

The best argument against the possibility of better clinical effectiveness of PCC-7 or PCC-8 is the estimation of rates of survival to hospital arrival after OHCAs attended by the services. While survival data from OHCAO Registry are not currently available yet for PCC-7 and PCC-8, it is possible to estimate the rates of the secondary outcome of survival to hospital after OHCA using the data provided by the prehospital critical care services. PCC-7 transferred patients to hospital after ROSC in 33 out of 90 cases (37%), PCC-8 in 214 out of 674 (32%). The vast majority of these patients are likely to arrive at hospital with a pulse (i.e. the secondary outcome of survival to hospital arrival). This compares to a rate of survival to hospital arrival of 36.4% in the primary analysis in Chapter 7. Given the similarity of rates of survival to hospital arrival in the data of Chapter 7 and the outstanding data, it is very unlikely that the rates of survival to hospital discharge (primary outcome) will be significantly different in the addition data.

Appendix E1: A reflection on the research aim, paradigm, and methods

During this 3-year doctoral research fellowship, I was lucky enough to receive a small amount of clinical training in prehospital critical care from the critical care team of Prehospital Critical Care Service One (PCC-1). Seeing the reality of out-of-hospital cardiac arrest (OHCA), and what happens during prehospital care, was a valuable frame of reference for this thesis.

One aspect of caring for critically ill patients in the chaotic and fast-paced prehospital environment is the importance of debriefing each case (Donald and Paterson, 2007). After the patient has been handed over to the receiving team at the emergency department and the equipment is cleaned and stored away, the prehospital critical care team sit down and examine each aspect of the care they provided in detail. The key questions guiding these debriefs are: What happened? What went well? What could we have done better? If we could go back in time, would we do anything differently?

With the data collected and analysed, results presented and discussed, I will now examine the approach I took to complete this thesis, borrowing from the practice of the prehospital debrief. The methods of each research phase were critiqued in detail in each of the corresponding Chapters 4 to 8. In this chapter, I will therefore mainly focus on the path from research aim to paradigm and methodology, which I introduced in Chapter 3, as well as the practical application of my chosen methods.

E1.1 The research aim

Throughout most of my formal and informal research training, teachers and supervisors emphasised the need for a good research question, frequently citing the PICO criteria (Bragge, 2010; Stone, 2002). In contrast, I do not recall having many discussions about research aims. This is possibly because most commonly, the research aims are essentially the research question, just formatted as a statement of intent. When I started thinking about this thesis, the research question I had in mind was

"In adult patients with non-traumatic OHCA, does prehospital critical care improve survival to hospital discharge, when compared to Advanced Life Support (ALS)?"

The reader will probably recognise this research question in Objective 2, Chapter 2. However, the research aim of this thesis is much broader than the original research question.

"To provide key stakeholders in prehospital care with the information required to guide the funding and configuration of prehospital critical care for OHCA ... "

The reason for this widening of the scope of the thesis was not a reconsideration of the research question itself, but rather the inclusion of additional research questions, represented in the other four objectives in Chapter 2. During the application for a doctoral research fellowship from the National Institute for Health Research (NIHR), experienced researchers suggested that the question of survival benefit from prehospital critical care was probably too narrow a question to receive grant funding. This was particularly true if the corresponding research design was to be observational. To strengthen the application and address the lack of randomisation, it was suggested that I add a qualitative exploration of the issue of randomisation as well as a health economics analysis. The inclusion of these two aspects completed the five objectives outlined in Chapter 2. I then retrospectively derived the research aim of the thesis from the objectives, once I had started the thesis.

Despite this somewhat convoluted way of defining the research aim, it proved to be an excellent guiding principle throughout the thesis. The emphasis on useful information for stakeholders helped me to focus the qualitative research and the final discussion on relevant aspects. On the other hand, I expanded the health economics analysis further than originally planned, in order to maximise the value of information provided. Fortunately, the research aim was sufficiently flexible and allowed me, for example, to plan most of the research addressing prehospital critical care interventions in the context of results from the earlier research phases. As a result, I believe that this thesis has achieved its aim, with each research chapter providing relevant information.

If I were to start again, I would probably try and establish an overarching research aim earlier on, as it did prove to be very useful. On the other hand, cycling through aims, objectives and research methods a few times early on in a PhD should not be regarded as an invalid approach to defining the research aim, and might be required to accommodate limitations of research design encountered along the way.

E1.2 The pragmatic research paradigm

In Chapter 3, I describe the research paradigm underlying this thesis; pragmatism. The initial appeal of the pragmatic paradigm was that it seemed to allow me to avoid thinking too much about the rather complex and often confusing fields of ontology and epistemology. This interpretation of pragmatism as "*it doesn't matter as long as it works*" has been criticised as a major weakness. If no fixed rules or assumptions exist, then what is left is not really a paradigm anymore (McDermid, 2018). Of course, pragmatism is a much more sophisticated philosophy than my initial interpretation, and addresses the ontological questions of what can be considered to be true (ontology) and how we can know (epistemology) and investigate (methodology) this truth (DeForge and Shaw, 2012).

At the beginning of this doctoral fellowship, the central ontological question of what is truth, or reality, seemed rather far removed from the subject of this thesis and the main objective of the effect of prehospital critical care for OHCA. However, it turned out to be one of the key issues of the qualitative research involving stakeholders in prehospital critical care and OHCA. Both the intervention and the condition I studied contained different truths, depending on the stakeholder group; see Table E1.1.

Table E1.1 Different realities of prehospital critical care and out-of-hospital cardiac arrest, by stakeholder group

Stakeholder group	Prehospital critical care	Out-of-hospital cardiac arrest
Patient and public involvement	Life-saving treatment	Life-changing event
Charities	Safety net in the case of sudden critical illness	Sudden critical illness
Commissioners	Expensive intervention	A small part of prehospital conditions
Researchers	Unproven intervention	A healthcare condition
Prehospital critical care providers	Interventions and expertise, professional identity	Aspect of daily work

As this picture of different realities emerged during the qualitative research phase, I was asked a difficult question by one of my supervisors. Which stakeholder group did I think was correct in their perception of reality? While certain stakeholder perceptions were more aligned with my personal points of view, I did not feel that disregarding others' realities would be an appropriate path to decision making. On the other hand, simply accepting the existence of different, and to a degree contradicting, realities would not be helpful to the process of finding common ground. These two options reflect the commonly adapted positivist and interpretivist paradigms described briefly in Chapter 3. In this situation, the pragmatic paradigm demonstrated its strength. Pragmatism sees reality as a constantly changing entity which can be reviewed, discussed and adapted in order to provide a workable framework (Broom and Willis, 2007).

Following this pragmatic interpretation of ontology, I did not focus on the validity or accuracy of each stakeholder group's reality, but looked for underlying mechanisms and identified common values. The knowledge of what stakeholders' perceptions are, how they are likely conceived and what connects them, despite the apparent differences, might allow stakeholders to negotiate towards a shared reality. I picked up on this notion of a negotiated reality again when discussing willingness-to-pay thresholds in Chapter 9.

In fact, the thesis stops short of definite recommendations on prehospital critical care for OHCA. This is partly due to uncertainty in the data, but also due to a recognition of the differences in stakeholders' realities. From a purely positivist perspective, this could certainly be interpreted as a weakness of the thesis, as the lack of clear recommendation would limit the usefulness of results. However, I would argue that in the complex setting of prehospital critical care for OHCA, strong and definite statements are likely to simply divide stakeholders even further, with detrimental effects on overall patient care. On the other hand, a more balanced, pragmatic approach can still provide guidance, while maintaining engagement and dialogue. I believe that this is ultimately a more successful path to better prehospital care for patients with OHCA.

But can we truly know the reality of stakeholders? Or the costs of prehospital critical care? The health economics analysis examines costs measured in monetary units and effects in quality-adjusted life years. But what about the impacts on bystanders, the reassurance of having modern technology available, the chance of sitting next to a close friend or relative for a few hours before they die in hospital, rather than being declared dead on scene?

My epistemological answer, based on pragmatism in this context, is that this thesis is unable, and never attempted, to provide a definite description of the reality of prehospital critical care for OHCA. Instead, what this thesis provides is a simplified but workable model of this reality.

"*Prehospital critical care has little to no effect on survival to hospital discharge following OHCA, and is associated with increased costs, when compared to ALS.*"

"The application of these results need to consider the uncertainty of the underlying data as well as stakeholders' priorities and perception."

None of these statements are likely to describe reality in full accuracy or detail. Furthermore, the strength of opinions expressed by stakeholders in Chapter 5 would suggest that the results of the thesis are unlikely to completely change their realities. What these result might achieve though, is to bring us closer to the truth.

In Chapter 3, I described the Justified True Belief (JTB) as a useful definition of knowledge . If we accept that truth either doesn't exist or it exists but is unobtainable, then the best we can do is to believe something to be true if there is strong justification for it (Starmans and Friedman, 2012). At the beginning of this thesis, I would argue, based on the findings from the qualitative research in Chapter 5, that many of the views regarding prehospital critical care for OHCA were just beliefs. What this thesis adds to the JTB model of knowledge about prehospital critical care for OHCA is the justification. Stakeholders can now discuss the evidence provided by my research, its limitations and interpretations. The resulting justified beliefs are not guaranteed to be true, but the chances that they are true are certainly higher than for the beliefs formed in the vacuum of evidence which existed prior to this thesis.

The third aspect to be considered within the pragmatic research paradigm is the methodology. Pragmatism is frequently associated with mixed methods approaches, a term I initially adopted for the methodology of this thesis, based on the fact that it included qualitative and quantitative methods (DeForge and Shaw, 2012; Creswell and Plano Clark, 2011). However, it was pointed out during the first progress review by the University of the West of England that I was not actually mixing methods, according to the research protocol at that time.

The qualitative research was to examine barriers to randomisation in this and similar research (see Chapter 5), whereas the main bulk of the thesis would address costs and effectiveness of prehospital critical care for OHCA. These were therefore two independent research questions and outcomes, only connected through their general subject and their inclusion in this thesis. In contrast, mixed methods would require that the researcher *"gathers both quantitative (closed-ended) and qualitative (open-ended) data, integrates the two, and then draws interpretations based on the combined strengths of both sets of data to understand research problems"* (Creswell and Plano Clark, 2011, p.124).

A suggested terminology for the methodology of this thesis was that of nested or embedded qualitative research within the larger quantitative research. However, these terms seem to be almost exclusively used when qualitative research recruits the participants in randomised trials, examining their experiences of participation or outcomes during the trial (Plano Clark *et al.*, 2013).

A possibly more accurate description of the methodology used for this thesis might be triangulation (Heale and Forbes, 2013). The term triangulation is used more generically to describe the use of different methods to investigate a phenomenon or address a question (Casey and Murphy, 2009). Considering the aim of this thesis, stakeholders require information about the effectiveness, costs, and configuration of prehospital critical care for OHCA, as well as an understanding of the context of this complex intervention (Craig *et al.*, 2008; National Institute for Health and Clinical Excellence, 2008). I used different methods to provide as much detailed information as possible to support this decision-making process.

In summary, the pragmatic research paradigm, with its focus on useful results and flexibility in regards to methodology provided a foundation for the research which suited the aim of the research as well as the limitations of prehospital care research.

E1.3 Methods

E1.3.1 Systematic review

The systematic review of the effectiveness of prehospital critical care for OHCA was beneficial for the rest of the project in two ways. It demonstrated a need for further research but also highlighted methodological issues which I was then able to address in my own observational research.

The most obvious alternative would have been to undertake a meta-analysis of the data identified in the review. In fact, when presenting the published review on a podcast, I was asked why I didn't (Laing and Fenwick, 2017). My answer to that question was slightly lengthy and convoluted. I would therefore like to take this opportunity to explain why a meta-analysis of the data would not have been helpful. This is the answer I wish I had provided on the podcast: *"A meta-analysis of the six observational research studies included in the systematic review would have shown a clear, statistically significant benefit from prehospital critical care. The reason for this is that one study (Yasunaga et al., 2010) would have dominated the results with a sample size much larger than all other five studies combined. Therefore, a meta-analysis would have likely mirrored the results of the largest study. What the meta-analysis would not have shown is sources of considerable confounding and bias present in these studies, which systematically strengthened an association between prehospital critical care and survival following OHCA. As such, a meta-analysis would have been a simplistic and possibly misleading summary of the existing evidence."* I made the same point regarding a meta-analysis of prehospital physician care for OHCA, which included a number of the studies included in my own review (Bottiger *et al.*, 2016; von Vopelius-Feldt and Benger, 2016a).

E1.3.2 Qualitative research of stakeholders' views

If I could go back and change aspects of this doctoral research project, the qualitative research would be a priority, in particular the data collection process. This was my first attempt at undertaking qualitative research, and I think this is reflected in the (lack of) rigor of the investigation.

Reading back through the original research protocol, I note that I planned recruitment of participants, conduct of the focus groups and analysis strategies in reasonable detail. However, there is little to no consideration of how to achieve internal and external validity. The reasons for this lack of a very important aspect of research was likely due to me not having read enough about qualitative research yet, and also due to the original objective, *" ... to describe the requirements that a prehospital RCT would need to fulfil in order to be feasible and acceptable ... ".* I consider qualitative research to exist on a spectrum of qualitative-ness (Denzin and Lincoln, 2000). Many of my doctoral research colleagues at the University of the West of England undertake complex and detailed qualitative research, such as *Exploring body perception and comfort after stroke: an interpretative phenomenological analysis* (Stott et al., 2017) or *Kurdish Generational Diasporic Identities; Perceptions of 'home' and Belonging within Families, among Iraqi Kurds in the UK* (Zalme, 2016). In contrast, I was just going to ask people why they did or did not approve of randomised controlled trials. My rather descriptive approach was very much on the less qualitative end of the spectrum, which made me not consider issues of internal and external validity in greater detail.

The need to venture deeper into qualitative analysis only became apparent after the first interview with the patient and public involvement (PPI) group. At this point, I changed the direction of inquiry but did not reconsider the methods of data collection. Going back, I should have arranged for a second researcher at each interview, taking notes and observing participants. I could have arranged for further focus groups or interviews after the first round, to feed back results from different stakeholders and elicit responses to these. The mixture of focus group discussions and interviews also caused great consternation during the peer review process of this research, however I am not sure I would have been able to change that without disproportionate amounts of effort.

In regards to data analysis, a more detailed plan for debriefing and independent review would have been helpful. I was very fortunate that the person transcribing the audio recordings took an interest in the study and provided an independent perspective.

These shortcomings made for a lengthy peer review process, and the final accepted manuscript had much of the fascinating results redacted in order to accommodate detailed descriptions of the less than elegant research design and its limitations (see manuscript attached to the hardcopy of this thesis). They also highlights a weakness of my application of the pragmatic research paradigm, which is outcome-, rather than process-oriented. I consider the results of my qualitative research to be useful and relevant, and I do not think they would be considerably different had I undertaken the research better. However, as a research project, its design is inelegant and contains flaws which could have been avoided with better planning.

E1.3.3 Health economics

While the focus on useful information, embedded in the aims of this thesis, helped me to focus my analysis on a few salient points during the qualitative research phase, it led to a wider scope of inquiry for the health economics aspect of the thesis.

The decision analysis model allowed me to incorporate data from different sources, include the data in a simplified model of a complex healthcare intervention and produce results that can guide stakeholders' decisions. Probably the most challenging aspect of undertaking this kind of analysis was identifying the relevant evidence and deciding how to incorporate it into the analytic model. I failed to make progress at this stage for a considerable number of days, overwhelmed by the complexity of the available data and the multitude of options as to how to use it.

After I realised that this was frustrating and non-productive, I decided to take a step back and start over with a more structured approach. I used systematic reviews of the literature, rather than ad-hoc searches (see Chapter 6). The searches were very basic and limited to the PubMed database, but they allowed me to clearly define a point at which I had exhausted the search and could therefore move on to the next stage. I also defined a hierarchy of the evidence, prioritising publications that were most relevant to modern care for OHCA in the United Kingdom (UK).

Once I had this structure in place, I managed to complete the synthesis of evidence for the decision analysis model. The modelling itself was helped considerably by the purchase of dedicated software (TreeAge Pro 2017, TreeAge Software). While, in theory, much of the analysis could have been done using Excel (Gray *et al.*, 2011), the potential for simple errors to create enormous distortions in data would have worried me. Even with the dedicated software, I still spent desperately long hours debugging the model and configuring the analysis process.

Despite these issues, I enjoyed this approach to health economics as flexible, transparent and outcome-driven. It is likely the right tool for many questions addressed by emergency medicine or prehospital care research.

E1.3.4 Propensity score analysis

Of all the methods I used in this thesis, propensity score analysis was certainly the method I invested most effort in, driven by the desire to cross the line from association to causation for prehospital critical care and survival following OHCA. An attractive feature of propensity score matching is that it makes intuitive sense and, when explained by outlining a few major steps, seems straightforward (Guo and Fraser, 2010). The difficulties start when considering the practical details.

As a relatively new analysis strategy, there is still considerable debate about how to actually undertake propensity score analysis correctly and efficiently (Holmes, 2014). First I learned that propensity score matching is only one of many options of propensity score analysis. Others are stratification, weighting or multivariate analysis. Next, the propensity score can be estimated by logistic regression including any combination of variables predicting the intervention, with or without interactions, square terms or logarithmic transformation, chosen by the researcher or by machine-learning algorithms (Guo and Fraser, 2010; Schonlau, 2005). Once the propensity score has been calculated, the researcher needs to make further decisions about the matching process (if matching is chosen as analytic strategy). The options here include: full matching; calliper matching; nearest neighbour matching in varying ratios and with or without replacement; optimal matching; Mahalanobis matching; others (Holmes, 2014).

Similarly to my experience during the health economics analysis, the plethora of choices felt paralysing initially. To make matters worse, any choice of analytic approach then needed to be implemented in my statistical software package (Stata SE, version 14, StataCorp), often with user-written codes. Making these choices therefore was not only about what was right, but also what was possible. For example, the command used for propensity score matching in Stata SE (version 14) is *psmatch2* (Leuven and Sianesi, 2003). Unfortunately, *psmatch2* only performs 1:n matching with replacement (see Chapter 7 for a discussion of this matching method). To undertake 1:3 matching without replacement, I had to write the code reproduced in Appendix C3, which runs *psmatch2* multiple times while removing matched cases of OHCA and storing the outputs after each run. Finding this solution took approximately 1 week and multiple failed attempts.

The choice of matching, rather than weighting or stratification, was based on the fact that this was the approach outlined in the protocol (von Vopelius-Feldt *et al.*, 2016). More importantly, the main advantage of propensity score matching over the other strategies or traditional multiple logistic regression is that the results of the statistical adjustments can be easily interpreted by the reader. Table 7.8 in Chapter 7 compares the distribution of prognostic factors between OHCA cases with prehospital critical care and ALS care. The reader can easily see that balance is improved for all factors, compared to the unmatched cohorts, but some residual confounding in favour of prehospital critical care remains. None of the other propensity score analysis methods allow for this kind of comparison, making the analysis in those cases somewhat of a black box procedure, where readers need to have trust in the researcher making the correct practical choices during the analysis (Kristensen and Aalen, 2013; Heinze and Juni, 2011).

When predicting the propensity score, I tried to use a machine-learning algorithm out of curiosity. However, the *boost* command in Stata SE (version 14) (Schonlau, 2005) resulted in such poor covariate balance that I abandoned any further attempts. Instead, I used different logistic regression models and a matrix approach to combine these with different matching strategies; see Appendix C2. Once I moved from trying combinations of the many methods at random, to a systematic evaluation of a few chosen methods, I managed to progress to a workable analysis strategy.

The final strategy used in Chapter 7 utilises the more basic choices available in propensity score analysis, a straightforward logistic regression to predict the propensity score followed by nearest neighbour matching with calliper. Reassuringly, I managed to meet and discuss propensity score analysis with the statistician Peter Austin, who has published extensively on the subject (Austin, 2011; Austin, 2009). He confirmed that, in his experience of propensity score in practice, the simple methods work well most of the time, mostly requiring only minor adjustments (personal conversation).

In summary, the advantages of propensity score matching, particularly over multiple logistic regression, are the underlying framework of causal inference, the separation of adjustment and outcome analysis, and the opportunity of checking that adjustment has been successful (Guo and Fraser, 2010). The price for these benefits is largely the time required to complete the practical aspects of the analysis. Out of curiosity, I ran a very basic multiple logistic regression model on my dataset, which included all prognostic factors for survival following OHCA. Table E1.2 compares the results of this analysis to those of the propensity score matched cohorts in Chapter 7.

Table E1.2 Odds ratios (95% confidence intervals) for survival to hospital arrival and survival to hospital discharge after out-of-hospital cardiac arrest with prehospital critical care, compared to Advanced Life Support, estimated by multiple logistic regression or propensity score matching

	Multiple logistic regression	**Propensity score matching**
Survival to hospital arrival	1.41 (95%CI 1.15 – 1.72)	1.39 (95%CI 1.10 – 1.75)
Survival to hospital discharge	0.95 (95%CI 0.70 – 1.29)	1.06 (95%CI 0.75 – 1.49)

The fact that the results for multiple logistic regression and propensity score analysis are, essentially, the same, is reassuring in regards to the likely accuracy of the primary analysis. On the other hand, I managed to achieve the same results with an analysis which took approximately 5 minutes to complete, as with an analysis which took 1 month to complete.

E1.3.5 Prehospital critical care services and interventions

The main challenge I faced when planning the analysis of prehospital critical care services and interventions was that the exact methods would depend on the distribution of data found as well as the outcome of the propensity score matching in Chapter 7. The second challenge was to recognise the limitations of statistical analysis, in particular regarding unmeasured confounding and small sample sizes (see Chapter 8 for a more detailed discussion). What proved to be very helpful was that I had formulated a number of hypotheses early on, when writing the introduction of the thesis, based on my previous research of prehospital critical care competencies (von Vopelius-Feldt and Benger, 2014). It was unlikely that individual prehospital critical care interventions would be the mechanism by which an improvement in survival rates might be achieved, while provider experience and transfer to an OHCA centre were more likely to result in benefits.

When I started the analysis, I complemented the testing of these hypotheses with questions resulting from the results of Chapter 7, mainly if the lack of benefit was due to the configuration of prehospital critical care services. I then matched the most appropriate method of analysis to each clinical question. I initially felt that the effort required for further propensity score analyses was too extensive. However, I also realised that the question of the effectiveness of specialised OHCA centres should ideally be addressed using propensity score analysis. Once I started this process, I realised that the codes I had written for the primary analysis could be adjusted and used successfully with only minimal additional work.

Having invested in the initial analysis, I now have a tool that I could use for future research in OHCA, addressing different questions.

E1.4 Summary

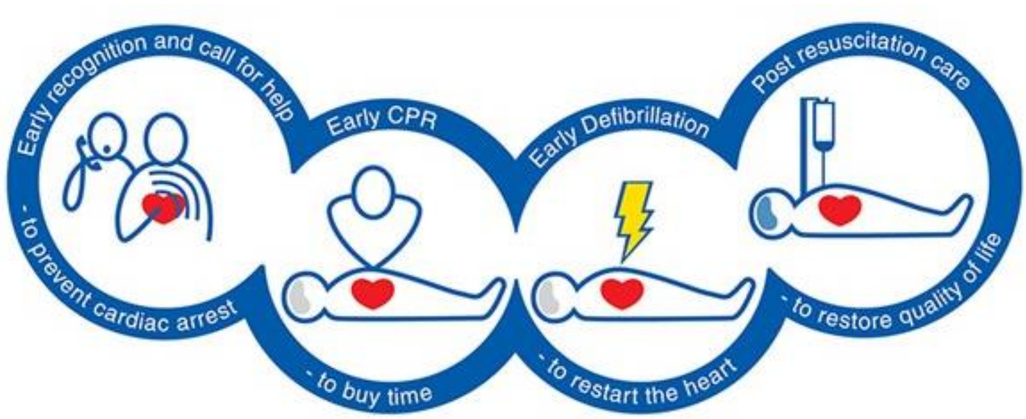
Over the course of this thesis, I was introduced to a new world of qualitative research, and acquired the basic tools to undertake further projects within a research team. I developed a deeper understanding of the possibilities of health economics, particularly the use of decision models to guide decision making. In regards to observational research and methods of statistical adjustment, I demonstrated detailed knowledge through the critical review of confounding and bias in the existing literature, successful practical application of propensity score matching and, importantly, an understanding of the limitations of various statistical methods. If I could go back in time, I would take the opportunity to spend more time and effort on the data collection for the qualitative research. The additional time required for this could be achieved by time-savings gained through the use of an early structured approach to data analysis in the health economics and propensity score analysis.

A major strength of this thesis is that a number of distinct objectives were addressed using different methods of varying levels of complexity and sophistication, as required to achieve the corresponding objective. Despite these individual and tailored approaches, all research presented in this thesis is embedded within the overarching research aim and supported by the consistently applied pragmatic research paradigm.

Appendix E2: A critical review of the Chain of Survival provided by the National Health Service

In Chapter 9 of the thesis, I discussed how survival following witnessed out-of-hospital cardiac arrest (OHCA) due to ventricular fibrillation (VF) in the population of this thesis is considerably less than that of similar population groups in high performing Emergency Medical Services (EMS) systems in other countries. Disappointingly, prehospital critical care does not seem to be a major potential contributor to achieving similar results in the United Kingdom (UK). In this appendix, I will therefore return to the concept of the Chain of Survival which I introduced in Chapter 1 and reproduced again in Figure E2.1. If prehospital critical care is not the right strategy to improve survival following OHCA, where should we concentrate our efforts instead? I will review each link of the Chain of Survival for the possibility of strengthening the link and achieving much needed improvement in survival following OHCA.

Figure E2.1 The Chain of Survival (Resuscitation Council (UK), 2015) with permission from Resuscitation Council (UK)



E2.1 Early recognition and call for help

Predictors of survival following OHCA can be divided into those amenable to intervention and those which are fixed and patient-specific, such as the patient's age and cause of the OHCA, for example. Of the modifiable predictors of survival following OHCA one of the most important, in this and previous research, is prehospital providers witnessing the OHCA (Nehme *et al.*, 2015a; Takei *et al.*, 2015). In the patient cohort of the primary analysis in Chapter 7, unadjusted survival rates were 21.0%, 9.3% and 2.8% if OHCAs were witnessed by

EMS providers, bystander or unwitnessed, respectively. For EMS providers to arrive before an OHCA actually occurs, warning signs need to be recognised by patients or relatives, communicated to 999 call handlers and recognised by the call handler. Finally, EMS response times need to be short enough for the provider to arrive before deterioration into OHCA occurs. While symptoms preceding OHCA can be nonspecific, they do occur before the majority of OHCAs (Nehme *et al.*, 2015b). Chest pain, dyspnoea or syncope have been identified as the three most prevalent prodromal symptoms for OHCA and should prompt urgent EMS activations (Nehme *et al.*, 2018; Hoglund *et al.*, 2014; Nishiyama *et al.*, 2013).

Nehme *et al.* (2017) showed that survival following OHCA increased after a public awareness campaign which stressed the importance of seeking medical attention if experiencing chest pain. Importantly, the incidence of OHCA also decreased after the campaign, suggesting that the arrival of EMS providers before OHCA not only improves survival but might prevent OHCAs occurring in the first place (Nehme *et al.*, 2017).

Even if EMS providers do not arrive before an OHCA occurs, the time from collapse to arrival of the first EMS provider is still of utmost importance. In my data, survival rates dropped from 8.8% for EMS providers arriving in less than ten minutes to 3.8% for EMS providers arriving after 10min, confirming findings from previous research (Rajan *et al.*, 2016; O'Keeffe *et al.*, 2011). Strategies to improve EMS response times include training both bystanders and 999 call handlers in correctly identifying OHCA and using computer-aided geospatial dispatch methods (Hardeland *et al.*, 2017; Hardeland *et al.*, 2016; Vaillancourt *et al.*, 2015). Of course, increasing the number and availability of EMS providers and ambulance response vehicles can dramatically reduce response times, however, this is associated with significant costs (Nichol *et al.*, 1996). Given that the only proven interventions delivered by EMS providers are CPR and defibrillation, strategies to deliver these interventions by people other than EMS providers have gained much attention (Bottiger *et al.*, 2018; Forrer *et al.*, 2002).

E2.2 Early cardiopulmonary resuscitation

Cardiopulmonary resuscitation (CPR) improves survival after OHCA, depending on early implementation (within seconds) and high quality of performance (Gallagher, Lombardi and Gennis, 1995). The effects of CPR on survival following OHCA are likely due to a reduction of ischaemic insult to the brain and other organs as well as prolongation of ventricular fibrillation until defibrillation can be achieved (Hasselqvist-Ax *et al.*, 2015; Swor *et al.*, 1995; Herlitz *et al.*, 1994). As many EMS systems around the world struggle with increasing demands, having EMS providers perform CPR on the scene within the required timeframe of less than a few minutes is not feasible (Association of Ambulance Chief Executives, 2017; Public Health - Seattle & King County, 2016). Early CPR is therefore now a task which needs to be achieved by members of the community, rather than healthcare providers (Kwon and Aufderheide, 2011).

In the research presented in this thesis, bystander CPR rates were 70%. Given that CPR can double survival rates following OHCA and does not require any equipment, many countries and organisation have invested in legislation or community programmes to teach CPR, mainly in schools (Perkins *et al.*, 2016b; Kanstad, Nilsen and Fredriksen, 2011). An economic analysis by Bouland *et al.* (2015) suggests that this is a cost-effective approach to improving survival following OHCA.

Another strategy now commonly employed in many EMS systems is the provision of CPR instructions from the emergency call handler to the caller, often referred to as dispatcher-assisted CPR. This change in practice is associated with minimal costs and has been shown to increase rates of bystander CPR and survival following OHCA (Song *et al.*, 2014; Bohm *et al.*, 2011). Importantly, research showed that, for bystanders to perform dispatcher-assisted CPR to the required high quality, previous formal training is required (Beard *et al.*, 2015).

A further step in the evolution of bystander CPR is the use of mobile phones to activate trained volunteers to attend suspected or confirmed OHCAs in their proximity. Frequently, these systems guide the volunteers to the location of the OHCA but also provide the location of the nearest public AED (Smith *et al.*, 2017; Ringh *et al.*, 2015).

E2.3 Early defibrillation

Together with CPR, defibrillation is the only intervention during the cardiac arrest phase of OHCA that has been proven to improve survival (Stiell *et al.*, 1999; Cummins *et al.*, 1985). The main limitations are that defibrillation is only applicable to the subgroup of OHCAs with a shockable cardiac rhythm (Soar *et al.*, 2015) and, as with CPR, benefits depend on application within a few minutes (Holmberg, Holmberg and Herlitz, 2000b).

Until approximately twenty years ago, defibrillation during OHCA required the presence of an EMS provider trained in either BLS or ALS (Becker *et al.*, 2008; Stiell *et al.*, 1999). Since then, improvements in technology have resulted in low-cost, semi-automatic defibrillators (AED) which can be used successfully by laypersons with minimal previous training (Hallstrom *et al.*, 2004). While there is no question about the considerable, life-saving effect of bystander-delivered defibrillation for individuals suffering from OHCA, rates of AED use by the public remain low in most countries, and was around 2% in my data (Agerskov *et al.*, 2015; Deakin, Shewry and Gray, 2014).

A major challenge is the fact that a majority of OHCAs occur in people's homes (75% in the population studied in this thesis). At the same time, public AEDs are unlikely to be cost-effective if installed in residential areas (Moran *et al.*, 2015), due to the relatively low frequency of OHCAs occurring per geographical area when compared to areas such as shopping malls, airports or sports facilities (Murakami *et al.*, 2014).

Initial strategies aimed at improving access to AEDs for OHCA included equipping police officers or fire fighters with AEDs (Nordberg *et al.*, 2015; Husain and Eisenberg, 2013). More recently, networks using mobile phone activation of volunteers either equipped with AEDs or provided with knowledge about the location of the nearest AEDs have been shown to shorten times to defibrillation in both urban and rural settings (Mauri *et al.*, 2016; Zijlstra *et al.*, 2014). More novel ideas to provide universal access are being considered as technology advances. Taxi companies which use mobile phone technology to direct their drivers have shorter response times than many EMS systems in urban areas and could therefore be equipped with AEDs (Friese, 2015). In rural areas, the use of drones to deliver AEDs is considered feasible (Claesson *et al.*, 2016). Finally, truly universal access to AEDs could be achieved through the development of simple, cheap, single-use AEDs affordable for every household (Rea, 2018).

E2.4 Post resuscitation care

While the first three links of the Chain of Survival now rely heavily on members of the public, post resuscitation care remains the primary task of healthcare providers. During the prehospital phase, there is no evidence that interventions beyond Basic Life Support (BLS) and timely transfer to an appropriate hospital provide further benefit (Sanghavi *et al.*, 2015; Stiell *et al.*, 2004).

In keeping with the literature showing a lack of survival benefit when comparing ALS and BLS for OHCA, my research showed no benefit when comparing prehospital critical care with ALS for OHCA. Once patients arrive at hospital, treatment in OHCA centres, which treat large numbers of patients with OHCA and provide optimal post-resuscitation care, is thought to result in better outcomes (Schober *et al.*, 2016; Heffner *et al.*, 2012).

Advances in technology and understanding of pathophysiology have created interest in further interventions such as extra-corporal life support (ECMO) (Johnson *et al.*, 2014) or tailored approaches to the post cardiac arrest syndrome (Sauneuf *et al.*, 2014). The most important limitation to all interventions in this fourth link in the Chain of Survival (with the exception of ECMO) is that they can only benefit patients for whom return of spontaneous circulation (ROSC) has been achieved and sustained long enough for the patient to be transported to hospital (25% of OHCAs in this study population).

E2.5 Identifying the weak link in the Chain of Survival

In this appendix, I provided an overview of initiatives and potential interventions aimed to strengthen each individual link of the Chain of Survival. While the aim of this thesis focused on funding decision regarding prehospital critical care for OHCA, probably more important is to achieve funding allocation which efficiently improves survival after OHCA. The question is therefore: which link of the Chain of Survival should be strengthened to improve OHCA survival, and how?

Table E2.1 compares the ambulance trusts that provided data for this research with three EMS systems which report excellent survival rates in the Utstein comparator group of OHCAs (bystander-witnessed VF OHCA). Due to differences in data collection, reporting, time intervals, sample sizes and patient populations, these numbers should be interpreted as indicative. Nevertheless, the comparison can provide information on probable weaknesses in the UK Chain of Survival, which resulted in worse overall outcomes in this research.

Table E2.1 Comparison of key features supporting the Chain of Survival for out-of-hospital cardiac arrest in four different Emergency Medical Services

	King County, USA	**Stavanger, Norway**	**Ticino, Switzerland**	**NHS trusts in this research**
Time period	2013 to 2015	2006 to 2008	2014	2016 to 2017
Community programmes for OHCA				
Community CPR programmes	*CPR training mandatory in schools*	*CPR training mandatory in schools*	*First responder network, activated by mobile phone*	*Variable through charities and foundations*
Other EMS systems involved in OHCA response	*Police first responders with AED*	*Fire service first responders with AED*	*Police and/or fire service first responders with AED*	*No formalised response by police or fire service*
Bystander CPR rates	68%	73%	70%	70%
Public AED use (includes police and fire service)	10%	-	7%	2%
EMS dispatch centre processes for OHCA				
Time to identify OHCA	1:15min	-	-	0:47min
Dispatcher-assisted CPR	Yes	Yes	Yes	Yes
Time from call to bystander CPR	2:56min	-	-	5:17min
EMS response times	BLS 5.5min ALS 8.0min	9.0min	9.9min	7.4min
EMS provider response to OHCA				
EMS response to OHCA	Two tier, BLS and ALS paramedics	ALS paramedics and critical care doctors or GPs	ALS providers	ALS paramedics +/- critical care services
Hospital treatment for OHCA				
In-hospital treatment	-	OHCA centre only	OHCA centre only	55% OHCA centres
Survival rates after shockable OHCA				
Bystander-witnessed	**56%**	**52%**	**55%**	**25%**
EMS-witnessed	**60%**	**-**	**-**	**56%**
References	Lewis, Stubbs and Eisenberg (2013) Public Health - Seattle & King County (2016)	Lindner *et al.* (2011)	Mauri *et al.* (2016)	NHS England (2018) Hawkes *et al.* (2017) Own data

NHS: National Health Service, CPR: Cardiopulmonary resuscitation, EMS: Emergency Medical Services, AED: Automated external defibrillator, ALS: Advanced Life Support

The first feature to note from Table E2.1 is that, despite less emphasis on community CPR programmes, rates of bystander CPR in this research are comparable to the three high-performing EMS. This is likely due to the effects of dispatcher instructions to provide CPR.

However, the quality of CPR is likely to be better in bystanders with previous practice (Beard *et al.*, 2015), which would have been achieved almost universally in EMS systems in countries with mandatory CPR training in schools. Such training might also improve the time bystanders require to recognise cardiac arrest and commence CPR, which was significantly longer in England compared to King County, USA.

CPR training in schools is currently non-mandatory in the UK, but has been proposed as part of a consultation on compulsory health education in all schools, from 2020 (Department of Education, 2018). In the meantime, an increasing number of charities, volunteer organisations, foundations and ambulance services are providing CPR training to members of the public (Perkins *et al.*, 2016b). Given that these efforts are largely uncoordinated and bound to be variable in which members of the public they actually reach, there is potential for improvement in community CPR teaching in the UK.

Second, the utilisation of police, fire service and/or mobilising volunteers seems to be associated with a higher proportion of public AED use. Ambulance trusts in the UK should therefore consider ways to improve AED availability for OHCA (Perkins *et al.*, 2016b). For example, London Ambulance Service has adapted both a police AED programme and a mobile-phone activated volunteer programme scheme in recent years (Metropolitan Police, 2017; Smith *et al.*, 2017).

Third, survival rates after VF OHCA that was witnessed by EMS providers was much more similar between King County and the English ambulance trusts, compared to the survival rates of bystander-witnessed VF OHCAs. This suggests that the weak link in the Chain of Survival in the UK is not post resuscitation care, be it prehospital or in-hospital. In addition, response times of ALS resources were similar across the four EMS systems, suggesting that this factor is less important in the presence of early BLS provided by bystanders, first responders or a first tier BLS EMS resource.

Based on findings from previous research and this thesis, I would suggest that prehospital critical care might have a role in the optimal delivery of post resuscitation care, but that this area should not be a priority for stakeholders looking to improve survival following OHCA.

Instead, the focus should be on community education to provide laypersons with the skills and confidence required to undertake high quality CPR, and strategies to optimise use of AED by first responders or members of the public.

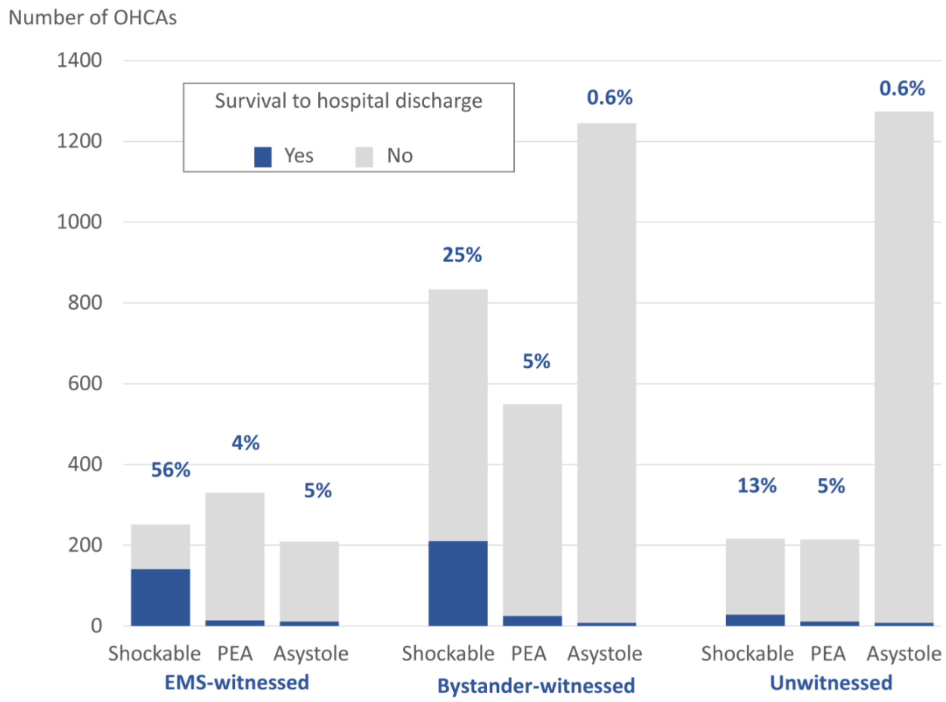
Of note, the recommendations based on the findings of this thesis as well as the topic and methods chosen for the research are in keeping with recommendations in the Cardiovascular Disease Outcomes Strategy published by the Department of Health (2013, p.7)

- *"Establish CPR training in all schools and mobilise relevant organisations to ensure this is done."*
- *"Identify simple consistent messages for the public, and achieve greater public awareness of what to do when faced with an out-of-hospital cardiac arrest."*
- *"Improve audit and set up a national defibrillator database."*
- *"Achieve a collaborative approach among stakeholders, including industry."*
- *"Ensure that all activities are evidence based and where evidence is lacking, call for appropriate research."*

E2.6 Recognising and accepting death

Amid the enthusiasm for bystander CPR and public use of AEDs, with survival rates exceeding 50% for bystander-witnessed, shockable OHCA in optimised systems, one should not forget that these interventions have benefit only for a subset of patients suffering from what we currently identify as OHCA (Perkins *et al.*, 2015a; Goto, Maeda and Nakatsu-Goto, 2014). Unfortunately, many patients treated for OHCA by bystanders and EMS providers continue to achieve no benefit from interventions, as they have likely made the transition from the reversible state of cardiac arrest to the irreversible state of death (Timmermans, 1999). Figure E2.2 provides a stark reminder that, despite the enormous efforts undertaken by researchers, healthcare providers and stakeholders, survival following OHCA is still very much dependent on factors which are beyond our control.

Figure E2.2 Survival to hospital discharge following out-of-hospital cardiac arrest, by witnessed status and initial cardiac rhythm.



OHCA: Out-of-hospital cardiac arrest, PEA: Pulseless electrical activity, EMS: Emergency Medical Services

Figure E2.2 demonstrates that the biggest group of OHCAs are patients with unwitnessed OHCA and an initial rhythm of asystole, which corresponds to no electrical activity in the heart. Within this group, only eight out of 1,274 patients survived to hospital discharge, which is similar to most previous research (Andrew *et al.*, 2014; Fukuda *et al.*, 2014).

Counter to intuition, an effective strategy to improve survival rates after OHCA on a system-wide level would be to not commence resuscitation in selected patient groups where survival chances are extremely low, thus excluding these patients from entry into OHCA databases (Nehme *et al.*, 2014). Reducing the number of futile resuscitations for patients at the end of their live would reduce EMS systems' and hospitals' resource use and would likely be in keeping with patients' and relatives preferences regarding the process of dying (Ranola *et al.*, 2015; Timmermans, 1999). The challenge to achieving this is to develop a diagnostic test which can distinguish irreversible OHCA or death from reversible OHCA on arrival of EMS providers (Grunau *et al.*, 2017).

Despite the issue not being clearly defined and infrequently discussed, clinicians generally accept the concept of an acceptable miss rate for diagnostic pathways for life-threatening healthcare conditions of 0.5% to 1% (Kene *et al.*, 2015; Pines and Szyld, 2007). For example, in the context of acute pulmonary embolism (PE) , a pathway which detects 99% of PEs, but misses 1%, would generally be accepted as sufficient (Pines *et al.*, 2012). This accepted miss rate can be justified by the fact that testing strategies which would achieve higher sensitivity for the condition would likely cause more harm than good (Pines *et al.*, 2012). Importantly, these concepts, when adequately presented and explained, are generally well accepted by patients in shared decision-making models (Gafni-Pappas *et al.*, 2018; Geyer, Xu and Kabrhel, 2014).

An important difference between the shared-decision models studied for conditions such as chest pain or suspected sub-arachnoid haemorrhage and the condition of OHCA with a very low chance of survival is that, in the first case, patients make the decision in a position of health and accept a risk of deterioration. In contrast, low risk OHCA patients are unable to make a decision at the time of the event, meaning that a conversation about the acceptable miss rate of not starting resuscitation needs to happen at community level, rather than with the individual. Furthermore, it is a decision between certain death without resuscitation and a chance of survival with resuscitation, rather than accepting a low risk of ill health at some point in the future.

Kahneman (2011) has extensively demonstrated that achieving a small chance of avoiding certain death is a much stronger motivator than accepting a small risk of death, even if the statistical probabilities of death were equal in both situations. While the ethical implications of these differences are beyond the scope of this thesis, the focus group discussion with the patient and public involvement group in Chapter 5 suggests that withholding resuscitation for OHCA would require a very high threshold for certainty that the intervention would indeed be futile.

Nevertheless, these are important conversations which need to involve clinicians and researchers, as depiction of life-saving treatments in the media is likely to raise unrealistic expectations amongst members of the public (Portanova *et al.*, 2015; Chen *et al.*, 2014).

The importance of basing such conversations on accurate data can be seen in the qualitative research in Chapter 5. At least some of the variation in stakeholders' views is due to strong perceptions of the benefit and costs of prehospital critical care for OHCA, in the context of a lack of reliable research evidence on this subject.

E2.7 Summary

Many initiatives aimed at improving the Chain of Survival for OHCA have been tried over the last few decades, and novel strategies, using new technology and big data, are being developed. Within the setting of ambulance services in the UK, the links in the Chain of Survival that should be strengthened as a priority are the provision of CPR and defibrillation by bystanders or first responders. Optimal post resuscitation care is important for patients who achieve ROSC after OHCA, but, within the limits of this exploratory analysis, is achieved with results similar to those of high-performing healthcare systems. Strengthening the Chain of Survival would likely lead to considerable improvements in survival for some patients with OHCA, mainly with a cardiac rhythm of VF. For large groups of patients with OHCA, current interventions are likely non-beneficial, and recognising these limitations is an important step to optimising care for patients at the end of their life.