WHY DO OUTCOMES OF HOSPITALISED PATIENTS WITH OUT OF HOSPITAL CARDIAC ARREST FROM ACUTE CORONARY SYNDROME VARY IN ENGLAND AND WALES?

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SUMMARY OF RESEARCH

Aim: To improve the quality and effectiveness of NHS care of patients who are admitted to hospital following an out of hospital cardiac arrest caused by an acute coronary syndrome.

Main research question: Why do outcomes vary after admission to hospital following an out of hospital cardiac arrest?

Study design: Retrospective analysis of an existing multi-centre prospective observational cohort study.

Data source: We will use the NHS national heart attack registry, the Myocardial Ischaemic National audit Project (MINAP), to identify a subset of patients (about 1.8%, estimated n = 15,000) who had a cardiac arrest recorded out of hospital and were admitted to hospital.

Inclusion criteria:

- Adults (aged >18 years)
- Out of hospital cardiac arrest (OHCA) due to an acute coronary syndrome (ACS)
- Initial resuscitation attempts successful leading to admission to an NHS hospital

Exclusion criteria

- 2nd or subsequent cardiac arrests
- In-hospital cardiac arrest only

Case identification: Cardiac arrest is defined as an “absence of signs of circulation and/or considered for resuscitation” (1). Careful scrutiny of MINAP definitions (2) shows that ‘first cardiac arrest’ in patients with ACS may be identified using a number of variables and/or combinations of variables. The optimal approach for case identification of OHCA will be ascertained and sensitivity and specificity reported.

Primary outcome: All-cause in-hospital mortality.

Secondary outcomes: Time to all-cause mortality and/or neurological outcome.

Impact of potentially modifiable predictor variables:

- Emergency Medical Services (EMS) transport time (3, 4)
- Use of an electrocardiogram (ECG) in ambulance/hospital
- The use of an early invasive strategy (including coronary angiography and / or percutaneous coronary intervention)(5)
- Time from first collapse to reperfusion
- Hospital volume of cases of ACS over study period (6-9)

Impact of potentially non-modifiable predictor variables (i.e. a subset of the confounding variables):

- OHCA occurring in presence of a trained health professional (including paramedic)
- EMS response time (10)
- Presence of a trained medic/paramedic during OHCA
- Location of OHCA
- History of diabetes mellitus
- Ethnicity (11)

Other potential confounders: co-morbidity, background risk variables, process variables
Using the rich data from MINAP, we will adjust for important confounders of survival from OHCA. These will include: age, gender, ethnicity and urban/rural domicile (from postcode), co-morbidity variables (e.g. previous acute myocardial infarction, chronic renal failure, chronic heart failure, diabetes), lifestyle variables (e.g. smoking status), results of investigations (systolic blood pressure, heart rate, raised cardiac troponin concentration), process variables (such as admitting consultant status etc.), core variables known to be important for surviving a cardiac arrest out of hospital (12, 13) and explore standardisation using established MINAP risk scores for stratification of patients with ACS (14-17),

Sample size: Within the complete MINAP database of just under one million events, there are an estimated 15,000 cases with OHCA hospitalised alive. Our initial work suggests that a sample of this size has adequate power to detect meaningful differences in the primary outcome, and will allow a detailed investigation of factors which may impact upon survival after OHCA (18).

Statistical analysis: Statistical analysis: We will impute values for the missing observations using multiple imputation via chained equations (14, 19), as has been suggested in the MINAP dataset (14). Sensitivity analyses will be performed to assess the robustness . We will fit multilevel models with a random effect term to test the hypothesis that the key explanatory variables and confounders explain the variability in outcomes.

Time schedule. The total time schedule of this study from setup to dissemination of results, with 60% FTE statastician, is 18 months.

Outputs and knowledge generation:

The project will produce four main outputs linked to the study objectives.

1) Define the epidemiology and outcome of patients who are admitted to NHS hospitals following successful resuscitation from out of hospital cardiac arrest that has been caused by an acute coronary syndrome

2) Report the relative contribution of potentially modifiable factors linked to the in-hospital pathway for these patients

3) Synthesise of the research findings from our team of experienced clinicians, those with responsibility for healthcare policy, patient and public representatives and expert methodologists to produce key recommendations for service organisation. If the data allow we will evaluate potential modi fications to health care system design and estimate the likely impact on heal th outcomes.

4) Prioritised summary of future research needs

Dissemination of the findings will be facilitated through publishing peer reviewed articles, national presentations, and through key NHS managers who are co-applicants on this application. We will liaise with international initiatives such as ILCOR to improve the definitional uniformity of factors affecting survival of cardiac arrest (12).

BACKGROUND AND RATIONALE

Out of Hospital Cardiac Arrest and the Chain of Survival

The sudden cessation of heart function (cardiac arrest) rapidly results in death unless treatment is instituted promptly. The commonest cause of a cardiac arrest in adults is an acute coronary syndrome (ACS) which is also sometimes referred to as a heart attack. In the UK, 60,000 people sustain an out of hospital cardiac arrest (OHCA) each year. Resuscitation is attempted in less than half of cases and less than one in ten people survive to leave hospital.(20, 21) OHCA is a life threatening, but potentially treatable disease – medical interventions can significantly increase the chance of survival from OHCA.(22)

The chain of survival describes a series of interventions that, if optimised, improve outcome from OHCA (figure 1)(23, 24) The first three links in the chain [(i) early access (recognition of cardiac arrest and prompt emergency response) then (ii) high quality cardiopulmonary resuscitation (CPR) (iii) early defibrillation] are focused on restarting the heart (referred to as return of spontaneous circulation). This part of the chain of survival is led by the ambulance service whilst the latter parts of care are managed by acute hospitals.

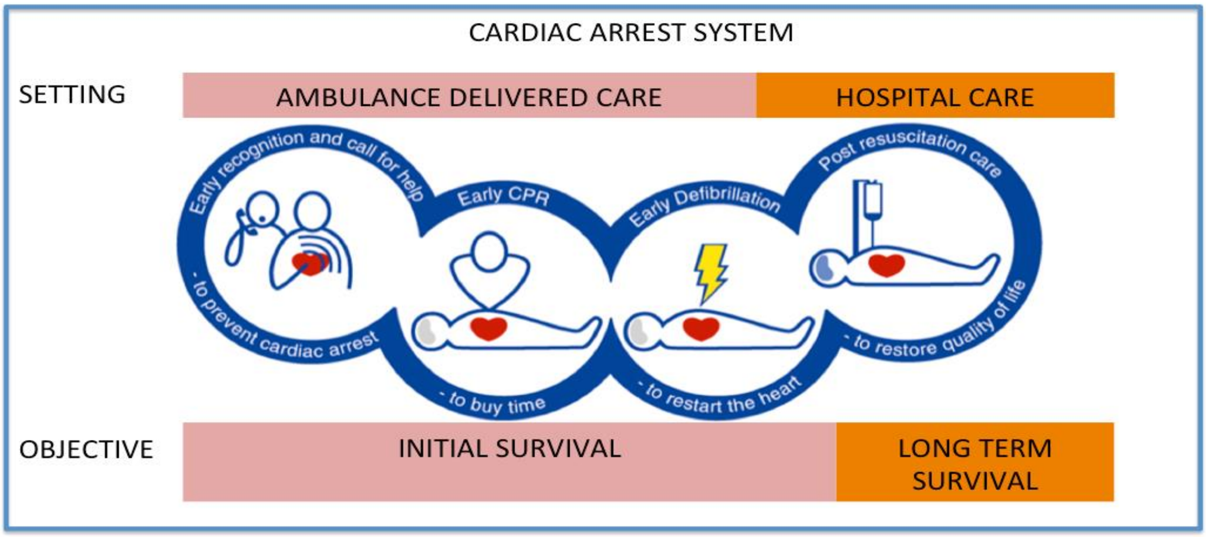

Figure 1: The Chain of Survival and relationship with different parts of the patient journey and their relative contributions to outcomes

If initial resuscitation efforts are successful the patient is admitted to hospital, where care focuses on the fourth link – post resuscitation care. It is this latter phase of care that is critical – it offers the best outcomes (long term survival with a good quality of life) for patients who survive to hospitalisation. Moreover, if a patient survives to leave hospital, many return to work & enjoy a sustained good quality of life.(25)

Variation in survival from OHCA

Concern surrounding substantial regional variation in outcomes from OHCA first arose in the mid 2000s when the Ambulance Service Association published data on survival from OHCA. This showed that initial survival rates from OHCA were dependant upon your geographical location and varied from 3 to 25% .(26) Yet, these data were never formally published.

In April 2011, the Department of Health included survival from OHCA as one of the key ambulance service quality indicators. Our analysis of data from the Department of Health National Quality Indicators identified a 6-fold variation (range 2.5 to 12%) in survival to hospital discharge rates from OHCA between ambulance services (see figure 2A).(27) Although the numbers recorded were small, standardisation for case mix using the Utstein population(1) (witnessed arrest, bystander CPR, shockable rhythm) did not reduce this variation; nor did it appear that the variation in outcomes were related to ambulance response times (Prof Cooke, National Clinical Director, personal communication). The House of Commons Public Accounts Committee review of emergency care provided by ambulance services (Sept 2011) reported wide variation both in costs and outcomes from care, and noted that there was little consistency in the methods for evaluating provider performance.(28) The report called for a better understanding of sources of variation in outcomes from OHCA. As a result, efforts to strengthen the pre-hospital care element of the chain of survival have commenced and include an examination of the impact of faster response times,(10) community cardiopulmonary resuscitation (CPR) education campaigns (e.g. BHF Vinnie Jones campaign), and CPR quality improvement initiatives.(20)

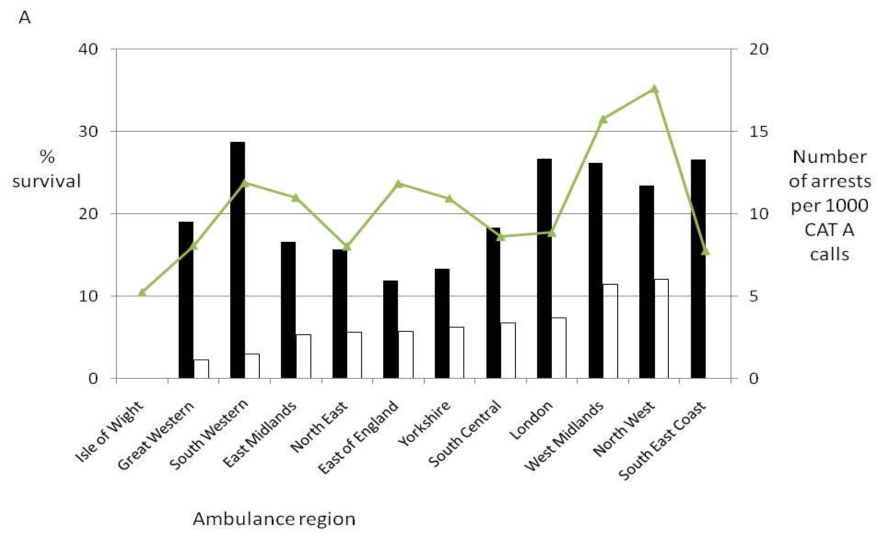

Figure 2A. Survival from OHCA by ambulance service. The left hand axis shows survival rates. Black rectangles show rates of initial survival. White rectangles show survival to hospital discharge. The small green/grey triangles relate to the right hand axis and report the number of OHCAs in each service relative to the number of emergency 999 calls (CAT A). Data reproduced from Perkins / Cooke EMJ 2012.(27)

The impact of hospital based post resuscitation care on long term survival

When the resuscitation attempt is successful, patients are admitted to hospital for on-going care. International data from resuscitation registries suggest that only a proportion of those patients resuscitated survive to go home from hospital, but also reveal significant variation in hospital survival rates ranging from 16 to 40% (29, 30). Similar findings are evident from the National Quality Indicator dataset for OHCA whereby survival to hospital discharge after initially achieving return of spontaneous circulation ranges from 10 to 50% (figure 2B). We found similar levels of variation in (range 0 to 50% survival to discharge relative to initial survival) in our PARAMEDIC randomised controlled trial in OHCA (data on file). While a degree of variation in survival rates will be associated with the effectiveness of pre-hospital interventions, the care delivered in hospital is central to patient longer-term survival and functional outcome.

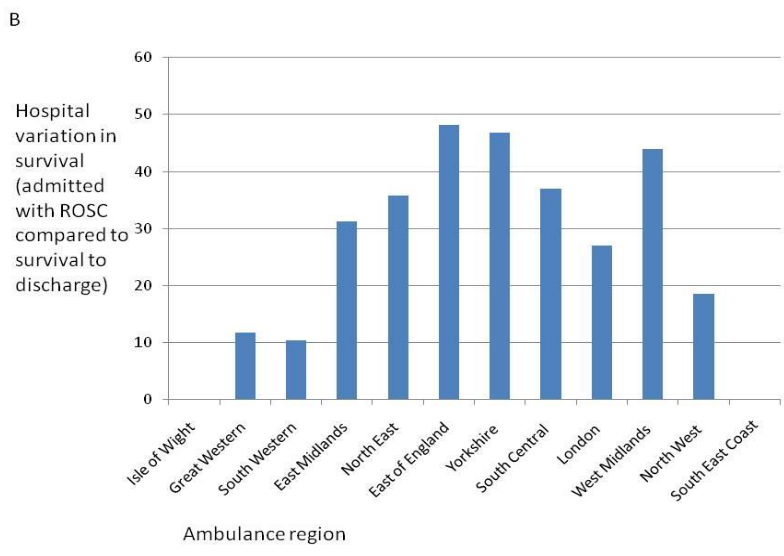

Figure 2B. Survival to hospital discharge for patients admitted to hospital alive after OHCA. There were no survivors on Isle of Wright. Survival to discharge data unavailable for SE Coast.

Potential modifiable factors

Following return of spontaneous circulation, a key decision for ambulance crews is to decide where to transfer the patient for on-going care. Currently, patients are transported to the nearest appropriate emergency department according to locally agreed protocols. They may, occasionally, be taken to medical assessment units with resuscitation facilities. This advice is based on the premise that receiving care in any hospital with an emergency department with critical care support is better than prolonged transfer times to more specialist care. This approach is informed by an observational study of over 10,000 patients' ambulance journeys to hospital. This study found that, on average, each 10km increase in straight-line distance was associated with a 1% absolute increase in mortality.(3).,Recent data, however, suggest that transfer time to hospital is a less critical determinant of outcome than the facilities available at receiving hospitals.(4, 31, 32) In two of these studies, based in urban settings, transfer to a specialist hospital with critical care and percutaneous coronary intervention (PCI) facilities outweighed any adverse effect on transport times(4, 31). Moreover, the ability of the EMS to perform a twelve lead ECG on the OHCA patient before reaching the hospital, may better inform healthcare professional as to whether to transfer the patient to the nearest hospital rather than a specialist (heart attack) centre.

Hospital volume of patients is associated with patient outcomes across a wide spectrum of health conditions ranging from trauma care,(6) through critical care(7) and primary PCI for ST Elevation Myocardial Infarction (STEMI).(8) Indeed, high volume, high throughput heart attack primary PCI-capable centres have lower early mortality rates(33). Yet, for OHCA, it seems that the provision of specialist services are more important than the impact of hospital volume.(4, 34, 35) Such specialist services mainly encompass the use of therapeutic hypothermia and availability of primary PCI. (5, 34, 36) Whilst implementation of therapeutic hypothermia is almost universal in UK intensive care units,(37) this practice is not widespread in Emergency Departments. There also remains variation in the availability and timing of PPCI (BCIS, 2011).

Based on a synthesis of these data, the USA is initiating a system of regionalised care for OHCA. They anticipate such a system will result in thousands of additional lives being saved each year.(38) It is difficult to estimate the effects of such a system of care in the UK, where environmental factors (e.g. disease prevalence, response times, distances travelled),Emergency Medical Services (EMS) systems (e.g. initial response time, ambulance staff skill mix, transfer time to hospital) and hospital configurations vary.

Exploiting the national heart attack registry to evaluate variation in hospital outcomes from OHCA

The Myocardial Infarction National Audit Project (MINAP) is a high quality national audit of process and outcome variables for patients presenting to all hospitals in England and Wales with ACS.(39) MINAP is unique in that it covers the entire patient journey from initial presentation in the community, through hospital care until final discharge and finally all-cause mortality. The database contains in excess of 800,000 patients and has so far provided substantial insights into sources of variation for patients presenting with an ACS ranging from mapping temporal trends,(40) to hospital related treatment factors.(9, 41), environmental exposure risks (42, 43), and secondary preventative drug effects (16).

Case-based data relating to factors affecting mortality after OHCA are scarce in England and Wales. A subgroup of MINAP (about 1.8% of the total patients) contains rich data relating to approximately 15,000 hospitalised patients with OHCA (estimated from a sample of MINAP data). This is of sufficient size and to allow ample power to detect even small effects from explanatory variables. Estimates of statistical power will be dependent on data completeness, which has been reported to be variable, as well as the chosen statistical method to deal with missing data (14, 15, 29, 39).

An application, in which release of data relating to 15,000 OHCA cases was was approved by the MINAP Academic Group on 6th February, 2012. A random anonymised sample of the MINAP data was pre-released for sole use toward this grant application. Whilst it did not contain all the data variables, it allowed a better comprehension of that data on which a modelling strategy could be based.. Release of the full MINAP dataset is conditional on successful funding of this grant application.

We confirm that there are no other plans within MINAP to study patients with OHCA. This project, therefore, provides a unique opportunity to examine the effectiveness of NHS care provided by ambulance services and hospitals when it comes to the effect of initial assessment (ECG), journey time to hospital, reperfusion methods and hospital volume on survival.

WHY THE RESEARCH IS NEEDED NOW

Each year 60,000 people sustain an out of hospital cardiac arrest in the UK. There is an urgent *health need* to improve outcomes from this condition – survival rates in the UK significantly lag behind the other countries where rates are as high as 25%. In the UK, less than one in ten people who sustain an OHCA survive to leave hospital. Many of these deaths will be avoidable.

The Commons Public Accounts Committee report "Transforming Ambulance Services" highlights the *expressed need* for research in this area. This report identifies wide variation in cost and outcomes for ambulance service delivered care. The report notes that "Performance will not be improved, nor will unwarranted variation be eradicated, until ambulance services have consistent information so that their performance can be compared with others".

MINAP provides an internationally competitive and unique opportunity to examine, at a national level using electronic health records, the full patient pathway for OHCA This is because it is population-based and covers both pre-hospital and hospital elements of ACS care. The use of standardised definitions and processes for mandated data collection provides an exceptional opportunity to explore outcomes across organisations.

Collating data from all acute hospital trusts in England and Wales, MINAP is one of the World's largest whole country databases of ACS. We know of no other such dataset which contains such a representative sample of data from patients presenting with acute coronary artery disease, over a period of many years. With statisticians at the University of Leicester, one of the applicants (IBS) has already explored the dataset in the context of research assessing the influence on survival of diabetes. Using multiple imputation to correct for missing data, and boot-strap statistical analysis, interrogation of MINAP identified recognised clinical and biochemical predictors of outcome, with no unexpected findings in this regard (Manuscript in preparation). This provides reassurance of the suitability of MINAP for addressing relevant clinical questions.

This project will *generate new knowledge*. It will present data (for the first time) on outcomes from OHCA for NHS patients that include data from both pre-hospital and hospital settings. The MINAP dataset contains some core elements of OHCA affecting survival (1) such as whether or not the cardiac arrest was witnessed by medical/ambulance staff, ambulance response time and journey time. In addition, MINAP contains data pertaining to hospital factors which significantly affect outcome from ACS (9, 17, 44, 45) which may also impact on survival from OHCA. In addition to describing case mix and outcomes, we will specifically examine the impact of potentially modifiable factors such as (i) journey time (ii) hospital volume (iii) specialist services (iv) methods and timing of critical interventions. We will do this in a way which ensures that the appropriate statistical techniques are used (including as multivariate imputation and multi-level modelling).

This project is a *cost effective* way to generate new knowledge about OHCA. It has taken over a decade and many hours of time of clinicians, administrators and IT personnel to collect the MINAP data and ensure it is accurate. Our project proposes to intelligently exploit a specific subgroup of this resource – thereby saving money and time on additional data collection. Furthermore, our study will be enhanced at no additional cost through use of data from a study into the quality of life of a subset of MINAP cases.

This multi-centre research proposal is grounded on the objectives of Health Services Research. It addresses a topic of major strategic importance, the results are likely to generate new knowledge and fill a gap in existing evidence. The research is embedded in NHS practice and we anticipate it will produce findings that will change practice. We have pulled together a strong team of clinicians, researchers, expert statisticians/epidemiologists and patient/lay representatives, and are working in partnership with the former Department of Health National Clinical Director for Urgent and Emergency Care which will ensure the project remains focused and relevant to health policy. It will also support future development of the national clinical quality indicator and ensure rapid adoption across the whole spectrum of policy relating to emergency care including improved outcomes, education and prevention.

Approaching this project from a national perspective will ensure that our findings are *generalizable* and relevant to the NHS. Our final project report will be designed to present information that is relevant to the NHS management community and will clearly highlight places where *prospects for change* exist.

AIMS AND OBJECTIVES

Aim

To improve the quality and effectiveness of NHS care of patients who are admitted to hospital following an out of hospital cardiac arrest caused by an acute coronary syndrome.

Objectives

To use the NHS national heart attack electronic health record registry to

1) report on the epidemiology and outcomes amongst patients admitted to hospital following successful resuscitation from a cardiac arrest caused by an acute coronary syndrome

2) identify the effect of modifiable factors, which could affect the outcomes of patients who are hospitalised following resuscitation from an out of hospital cardiac arrest (OHCA)

3) produce recommendations for optimising hospital organisation of services

4) produce prioritised list of recommendations for further research in this area

METHODS

Research methods

Study design: Retrospective analysis of a multi-centre observational cohort study.

Data source: We will exploit the existing MINAP dataset of patients with an ACS (2, 15, 17, 40, 46, 47). Analysis of a random sample of data, supplied my MINAP to inform this study, confirmed that a subset of people within MINAP (about 1.8%, estimated n= 15,000) will have a cardiac arrest event recorded out of hospital and had a return of circulation at hospital admission.

Inclusion criteria:

- Adults (aged >18 years)
- Sustained an out of hospital cardiac arrest due to an acute coronary syndrome (ACS)
- Initial resuscitation attempts successful leading to admission to hospital

Exclusion criteria

- 2nd or subsequent cardiac arrests
- In-hospital cardiac arrest only

Case identification: Cardiac arrest is defined as “Absence of signs of circulation and/or considered for resuscitation”(1). Careful scrutiny of MINAP definitions(2) shows that ‘first cardiac arrest’ in ACS patients may be identified using different variables and/or combinations of variables. Once we have received all variables from MINAP (currently we received a subset), we aim to identify cardiac arrest events in the most inclusive manner (i.e. MINAP variables 3.10 or 3.13 or 3.14 or 3.15 or 3.16)(47). The best approach for case identification of cardiac arrest within MINAP will be ascertained. If possible, we will report their sensitivity and specificity.

All MINAP’s case identification variables of cardiac arrest are marked as not essential. The latter has implications for the completeness of the MINAP dataset for this specific subgroup of patients who had a cardiac arrest. In the wider context of patients with an acute coronary syndrome completeness of data is better known and has been reported to be variable (27, 31-33).

Primary outcome: All-cause in-hospital mortality.

Secondary outcomes: Time to all-cause mortality and/or neurological outcome (dependent on missingness pattern of the latter).

Impact of potentially modifiable predictor variables

The following variables may influence long-term survival after an initially successful resuscitation attempt:

- EMS transport time
- ECG in ambulance/hospital (3, 4)
- The use of an invasive strategy (e.g. percutaneous coronary intervention)(5)
- Collapse to reperfusion time
- Hospital volume(6-9)

Impact of potentially non-modifiable predictor variables (i.e. a subset of the confounding variables):

- Cardiac arrest occurring in presence of a trained health professional (including paramedic)
- EMS response time (10)
- Presence of a trained medic/paramedic during cardiac arrest
- Location of Cardiac arrest
- Prior diabetes
- Ethnicity (11)

Other potential confounders: co-morbidity, background risk variables, process variables:

We will adjust for important confounders of cardiac arrest which are recorded in MINAP such as age, gender, ethnicity and urban/rural domicile (from postcode). Established risk scores for stratification of ACS patients, such as the GRACE variables (14), will probably not be applicable to those who sustain cardiac arrest, but this effect will be explored.

We will also consider other important confounders that MINAP contains, such as; co-morbidity variables (e.g. previous acute myocardial infarction, previous chronic renal failure, previous heart failure, previous diabetes), lifestyle variables (e.g. smoking status), risk variables (family history of CVD), screening variables at hospital (systolic blood pressure, heart rate, raised troponin) and process variables (such as admitting consultant status etc.).

Mapping of the MINAP data dictionary to the international ‘Utstein’ fields of core variables known to be important for surviving a cardiac arrest out of hospital (12) has shown that not all Utstein core variables are explicitly recorded in MINAP (Table 1), and we will explore whether it is feasible to derive some of the remaining core Utstein fields using the MINAP resource.

TABLE 1 Mapping the MINAP data dictionary (2, 47) to the international 'Utstein' fields (12)

Core Utstein template variables (for people with out of hospital cardiac arrest)	**Found in MINAP?**	**Which MINAP variables?**
Date/time call to EMS received	In MINAP	3.02
Patient identifier	In MINAP	1.02, 1.03, 1.04, 1.05, 1.06
Sex, age, ethnic origin	In MINAP	1.06, 1.07, 1.12
Date/time of witnessed/monitored arrest	In MINAP	3.13
Witnessed not witnessed	EMS witnessed may be derived in MINAP	3.13 and 3.14
Aetiology	ACS syndrome	
Location of arrest	In MINAP	3.14
EMS involvement	May be derived in MINAP	3.14, 3.16
Nature of resuscitation (e.g. chest compression, etc.	Not in MINAP	
First monitored rhythm	In MINAP	3.15
Date/time of 1st monitored rhythm assessment	Not in MINAP	
Date/ time of first CPR attempt	Not in MINAP	
Date/time of first defibrillation attempt	Not in MINAP	
Any ROSC? (yes, no, do not know)	May be derived in MINAP	3.16
Survival- sustained ROSC until admission	May be derived in MINAP	3.16
ROSC and admitted to ED/ICU	May or may not be derived in MINAP?	3.14
Survival to hospital discharge	May be derived in MINAP	3.16
Neurological outcome at discharge	May be derived in MINAP	3.16

Emergency Medical Services =EMS

Further detailed variables selection will be scheduled in our set up phase when multidisciplinary teams have been convened. This will allow discussions between specialist experts of the MINAP database (who know about missingness patterns)(14, 15), cardiac arrest experts(16, 24, 27, 42, 48), and experts in statistical imputation/modelling(13, 18, 49-52). This will be further backed up by a literature review.

Sample size:
Within the complete database of MINAP of just under a million events, an estimated 15,000 cases exist for patients admitted to hospital after out of hospital cardiac arrest. To prepare the proposal, MINAP provided us with 84,194 cases from the MINAP dataset. These cases were selected randomly and are slightly less than 10% of the whole MINAP dataset. Hereafter, we refer to these cases as the sample dataset.

We identified 1,431 cardiac arrest cases from the sample dataset. For the primary outcome (in-hospital survival), 345 patients (24%) died in hospital, 847 patients (59%) were discharged while for the rest of the patients, data on whether they died in hospital or were discharged are missing. Data on status and data of censorship will be available in the full MINAP database, to be release upon successful award of this application. Therefore, taking the most conservative approach (assuming the sample dataset is representative of the whole dataset), we expect to identify approximately 14,310 patients experiencing cardiac arrests with 3,434 (0.24x14,310) dying in hospital. As a rule of thumb, for logistic regression and Cox regression models, it is recommended in literature that there are 10 events (in our case the event that a patient dies in hospital) for each predictor variable.(18) Therefore, because we expect 3,434 events, we have enough events to model the MINAP data to answer our research questions. The MINAP data will be sufficient to detect a rate difference of at least 4% or more with at least 90% power at a 5% significance level and under some configuration of rates, the data may be enough to detect a rate difference of 2% with sufficient power. For example, for a binary predictor variable such as smoking, the MINAP data will be sufficient to detect a rate difference of at least 4% or more with at least 80% power at a 5% significance level and under some configuration of rates, the data will detect a rate difference of 2% with almost 70% power. The table below shows an example of the power for testing the difference in rates of death at 5% significance level when rate difference is 0%, 2%, 4% or 6% and the prevalence for non-smokers is 0.10, 0.20, 0.30 or 0.50. We expect higher powers than in the table because the powers are based on assuming conservative standard errors and 10% of MINAP data in sample dataset.

Power for some scenarios

Prevalence of non-smokers	Rate of death for active or past smokers	Rate of death for non-smokers			
		0.46	**0.48**	**0.50**	**0.52**
0.10	**0.46**	5	29	81	99
	0.48	29	5	28	81
	0.50	81	29	5	29
	0.52	99	81	30	5
0.20	**0.46**	5	47	97	100
	0.48	48	5	48	97
	0.50	97	47	5	47
	0.52	100	97	48	5
0.30	**0.46**	5	58	99	100
	0.48	59	5	59	99
	0.50	99	59	5	59
	0.52	100	99	59	5
0.50	**0.46**	5	67	100	100
	0.48	66	5	65	100
	0.50	100	67	5	66
	0.52	100	100	66	5

Data accuracy: The MINAP data application contains error-checking routines, including range and consistency checks, designed to minimize common errors. MINAP provides detailed guidelines for data entry and provides a dedicated helpdesk to support problems regarding clinical definitions and data entry in a variety of clinical scenarios. MINAP also performs an annual data validation study to assess the agreement of data held on the NICOR servers. Hospitals are required to re-enter data from case notes in 20 key fields (different fields to the data completeness fields, with some overlap) in 20 randomly selected non-STEMI records in an online data validation tool. Agreement between the original and re-entered data is assessed for each variable and each record. Reports showing the agreement of each variable compared to national aggregate data are sent to hospitals to allow them to identify areas for improvement. 95% of eligible hospitals in England, 69% in Wales and 2 hospitals in Northern Ireland participated in this year's data validation study. The median score for 2011 was 95.5% (IQR 89.5-98) maintaining the high standards of 2010. Thus, people have worked hard to ensure its accuracy, despite its acknowledged data missingness at times.

Missing data: There are two statistical issues that arise while analysing the MINAP data. The first is how to handle the missing data and the second is the strategy to use to model the data. The MINAP data is incomplete because for some patients, there are missing observations for the outcomes and/or covariates (14). We assessed missingness for several variables in the sample dataset. For example, for the primary outcome and the predictor variables ethnicity, smoking, blood pressure and heart failure, approximately 17%, 25.9%, 20.5%, 17.6% and 17.9% of data are missing respectively. These percentages of missing data are similar to the percentages identified in a previous assessment of missing data in the MINAP dataset (14). From the sample dataset, the percentage of complete cases (the percentage of the patients without any missing observation) is 45% so that complete cases analysis leads to discarding a high proportion of data and this may lead to bias. To avoid this, we will impute values for the missing observations using multiple imputation via chained equations (14, 19, 53), as it has been suggested to impute missing values in the MINAP dataset (14). For variables that correspond to previous medical conditions and standard drug therapies, we will use default imputation, where we impute a "No" unless other data suggest otherwise. We will use predictive mean matching for continuous variables, logistic regression for binary variables and polytomous regression for multi-category variables. The variables to be included in the model are the outcome variables, predictor variables, confounding variables that will be used in the analysis and auxiliary variables that can predict the missingness. Interactions, in particular between sex and year of admission, will be incorporated by imputation by splitting due to the large numbers of variables (14). To reflect the uncertainty about the imputed values, 25 imputed datasets will be created using the MICE package in the R statistical program. Each of up to 25 imputed datasets will be analysed separately using standard statistical methods as described below and the model estimates pooled into an overall estimates of multiple imputation and associated standard error using Rubin rules (50, 54). Sensitivity analyses will be performed to assess the robustness of the results to the missing data methods used and assumptions made (53, 55).

Modelling strategy: To account for the hierarchical structure of the data, such as patients within a hospital, a random effects (multilevel) logistic regression model will be used for the binary primary outcome of whether a patient survives to discharge or not. A random effects (frailty) regression model will be used for the secondary outcome of time to all-cause mortality. The applicability of Cox proportional hazards model or a parametric model such as the accelerated failure time Weibull model will be determined and most appropriate model employed. The aim of the modelling will be to identify modifiable explanatory factors which significantly affect the primary and secondary outcomes using models that adjust for the other explanatory variables and confounders such as age and gender in the final model. Some key modifiable explanatory variables and confounders may be correlated, and including highly correlated key explanatory variables and confounders in the same model can lead to erroneous conclusions of how the modifiable explanatory variables affect patient outcomes. This problem of multi-collinearity between variables will be assessed using correlations, scatter plots and stepwise model building strategy to determine how the effect estimates change when including one or both of the variables in the model. For two highly correlated explanatory variables, we will choose to include in the model the explanatory variable with the strongest relationship with outcome. If the number of confounders is large, to reduce the process of assessing multi-collinearity, we will employ principal component analysis to construct new independent variables from the confounders (except modifiable variables) and use them in the modelling strategy. In addition to the main effects, interaction terms for prognostic factors and confounders and time will be considered but only the statistically significant terms retained. The regression model parameters will be used to test the hypothesis that the explanatory variables predict patient outcomes.

We will fit multilevel models with a random effect term for hospital to test the hypothesis that the key explanatory variables and confounders explain all the variability in the outcomes or whether the outcomes vary in England and Wales. Bootstrapping will be used to obtain the 95% confidence interval (CI) for the random effect term and if the upper limit of the 95% CI is below 0.366 (this corresponds to an intraclass correlation of 0.1 for latent formulation of a binary outcome (56), we will conclude that the key explanatory factors and confounders explain the variability in outcomes in England and Wales.

DISSEMINATION AND PROJECTED OUTPUTS

The project will generate new knowledge about the level of variation in outcomes following initially successful resuscitation from OHCA by ambulance services. It will specifically evaluate the relative contribution of potentially modifiable factors linked to the in-hospital pathway for these patients. The output from this project will provide a platform to model the effects of reconfiguring care pathways, designed to optimise patient outcomes. This project pulls together an expert team of clinicians, managers, methodologists and health service users. The team have a strong track record of high quality research and are well placed to synthesise the findings of this project into recommendations about service organisation that have the potential to lead to tangible benefit to health service users.

The specific outputs that will be produced will be as follows:

(1) The epidemiology and outcome of patients who are admitted to NHS hospitals following successful resuscitation from out of hospital cardiac arrest that has been caused by an acute coronary syndrome.

(2) The relative contribution of potentially modifiable factors linked to the in-hospital pathway for these patients. This will serve as a platform to model the effects of reconfiguring care pathways, designed to optimise patient outcomes.

(3) Key recommendations for service organisation. Our team of experienced clinicians, those with responsibility for healthcare policy, patient and public representatives and expert methodologists will synthesise the findings from this analysis into key recommendations for service organisation. If the data

allow we will evaluate potential modifications to health care system design and estimate the likely impact on health outcomes.

(4) Prioritised description of future research needs. We will review the findings of this research and assess if further research is required. In the event that further research is required we will prioritise the most pressing future research needs.

To ensure effective knowledge mobilisation, our dissemination strategy will be designed to meet the needs of three distinct groups – healthcare providers (ambulance staff, hospital doctors and nurses); commissioners / policy makers and patients and public. We will target healthcare providers through a number of routes – presentations at regional / national meetings, publication in open access peer reviewed journals, webcasts review articles. These mediums will be used to disseminate the research findings with a strong emphasis on the implications of these findings for individual patients and for clinical practice.

Briefings for commissioners and policy makers will be constructed to present the potential health gains at a population level (e.g. number of lives saved, quality of life) for example if the findings suggested hospital type / volume was a strong predictor of outcome, the effect of regionalising care at cardiac arrest treatment centres. We will specifically target commissioners e.g. Clinical Commissioning Groups and professional organisations through our links with Department of Health Urgent and Emergency Care Policy Team and the College of Emergency Medicine, Faculty of Pre-hospital Care, Ambulance Service Medical Directors Group, Joint Royal Colleges Ambulance Liaison Committee, Intensive Care Society, British Cardiovascular Society, and Resuscitation Council (UK).

One of our lay representatives keeps us focused on the desire of patients to receive healthcare close to their home and community. This project will generate key information about the benefits and disadvantages between local compared to regional healthcare provision. With the support of our lay representatives and the communication team at Warwick University we will ensure that the key messages from this project are presented clearly, concisely and in plain English. We will use a variety of platforms to disseminate our findings jointly with the Communications Department at Warwick Medical School. This team has excellent relations with local and national media organisations. Work from our group has been showcased in various settings (e.g. local TV, Newspapers, BBC News, The One Show, Radio 4) allowing the impact of our work to extend beyond traditional healthcare boundaries. In addition, we will produce and disseminate lay summaries through our institutional websites and partner PPI groups (e.g. MINAP user group, Resuscitation Council (UK) patient advisory group).

PLAN OF INVESTIGATION AND TIMELINE

Project plan/ timeline

Whilst the dataset is unique and the multidisciplinary team strong (see below), MINAP is known to contain missing data, which are best handled by statisticians/epidemiologists/clinicians with the right expertise level that are aware of some of the pitfalls and benefits of such data. The latter is reflected in the composition of the management committee and the time schedule of the project which are based on the availability of dedicated and expert statisticians(13-16, 27, 29, 42, 48, 50, 51).

A detailed project plan (based on the time schedule below) will be developed at the start of the project (see below).

Our proposed study milestones are:

Based on 60% FTE statistician

Set up phase- Month 0-3	Setting up committees, apply to MINAP, IT preparations
• Milestone 1 (Month 3-4)	Receive MINAP data, data coding, raising queries
Implementation phase- Month 4-14	
• Milestone 2 (Month 4-8)	Case identification, data manipulation, preliminary analyses
• Milestone 3 (Month 9-16)	Analyses, imputation and sensitivity analyses
Dissemination phase 16-18	

• Milestone 4 (Month 17)	Draft report ready
• Milestone 5 (Month 18)	Dissemination: Verbal presentation and final report

Timeline based on 60% full time equivalent of an expert statistician

Month	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Management comm.																		
Steering committee																		
Apply MINAP																		
IT preparation																		
Case identification																		
Data manipulation, preliminary analyses																		
Analyse: impute																		
Sensitivity analysis																		
Steering consensus																		
Write up																		
Dissemination																		

ETHICS APPROVAL

This application involves a secondary analysis of an existing dataset. Data are collected and held by MINAP project team with authorisation by the National Information Governance Board.

The University of Warwick have strict information governance policies and procedures which will be strictly adhered to. Although ethical approval from NRES is not needed if the data is anonymised, such as the data we will be applying for in MINAP in the NRES guidance, we will submit our application to the University of Warwick's expedited and rigorous Biomedical Research Ethics Committee (BREC), because this is a requirement for all health related studies involving human participants. Data will be handled and stored securely according to the Warwick Clinical trials Unit standard operating procedure.

MINAP is one of several cardiac audits which use a highly secure electronic system of data entry, transmission and analysis developed by the Central Cardiac Audit Database (CCAD). This system uses encryption of patient identifiers to allow secure transfer of data between hospitals and central servers and allows linkage with the Office of National Statistics for tracking mortality. To further protect patient information we will not seek personal identifiable information from MINAP.

The bespoke System Level Security Policy submitted to the MINAP Academic Group by our specialist Warwick Clinical Trial's s programmers and Quality Assurance Managers alongside the MINAP application has been approved.

PROJECT MANAGEMENT

Project oversight

The project will be overseen by a steering committee comprising representatives from the Resuscitation Council (UK) (Perkins, Quinn), Study Coordinating Centre (TBC), Statistical and epidemiological Expertise (Marshall, Kimani, Gale), Ambulance Service National Medical Directors Group (John Black, South Central Ambulance, Emergency Physician and former Department of Health National Clinical Director until October 2012(Cooke) and experts from MINAP (Squire, Quinn, Gale,) and patient / public representative. The steering committee will provide oversight at each stage of the project. We will make use of Webinar technology when possible to minimise carbon footprint. The Steering committee will be responsible for sign off the final statistics analysis plan, approve publications and assist with disseminating the findings of the project. The steering group will meet face to face in the final quarter of the project to review the results and to synthesise the main messages from the research that are relevant to healthcare policy and organisation. All co-applicants will contribute as appropriate during the lifetime of the programme.

Management team

Under the overall leadership of Prof Gavin Perkins the project will be managed on a day to day basis by TBC and delivered on time and to budget. Local project management meetings will take place initially weekly (and latterly at least monthly) to ensure the project sticks to the agreed milestones. Dr Gale, NIHR Clinician Scientist and Honorary Consultant Cardiologist will sit on the management team and will guide us through some of the common pitfalls of MINAP to avoid duplication of effort.(15, 29) Dr Andrea Marshall, an experienced statistician who specialises in imputation,(50, 51) will advise Dr Peter Kimani who will be the dedicated experienced statistician.(13, 18)

Any deviations from the agreed project plan and time line will be identified and analysed using the principles of root cause analysis and a recovery plan agreed. This process of active management has been shown to work effectively in previous studies, ensuring that projects are delivered on time and within budget.

Careful selection of the research team and the complementary skills and experiences they have will ensure that this registry can be delivered effectively. Staff will be primarily based at Warwick Clinical Trials Unit. We will have regular face to face meetings, with at least 6 formal meetings per year.

PATIENT AND PUBLIC INVOLVEMENT (PPI)

We have sought to embed patient and public involvement throughout this application in line with the principles of INVOLVE (2012). During the planning stages of the application we have benefitted from the insights provided by Suzanne Shale (Past Chair of lay group of College of Emergency Medicine and academic researching patient experience), and Mr John B Long, former Secretary General for the Royal Life Saving Society (charity), two experienced PPI representatives who have previously supported numerous other research. The application was developed in partnership with these individuals. It became clear during the early phases of project development that key priorities from PPI perspective were the quality of life after survival from cardiac arrest and the effect of journey times to hospital (considering the burden this places on the family and friends of victims of cardiac arrest). It is for this reason that we have expanded our initial proposal to incorporate quality of life of survivors. Whilst the MINAP data dictionary does not capture direct quality of life information, patient’s neurological outcome / neurological dysfunction is part of MINAP and touches on aspects of quality of life. Investigating neurological outcomes was already part of our strategy as one of the outcomes. These themes will be explored further once we receive MINAP data, and the findings will be discussed further in the steering committee of which our patient representative is part. We will further explore Health Related Quality of Life with our co-applicant Dr Chris Gale who has completed accrual of 5555 patients hospitalised with ACS at 49 centres in England (2010-1013) – recording EQ5D data at 4 time points up to 1 year after presentation which are electronically linked to MINAP and Office of National Statistics (the EMMACE-3 prospective study).

The project will benefit from the on-going engagement and insights of these PPI representatives through their active involvement as full members of the project steering group. As in previous projects (e.g. HTA funded LUCAS trial, HSDR Do Not Attempt Resuscitation Project), our PPI members will play an active role in disseminating the output from this project through their established local and national networks.

EXPERTISE

Prof Gavin Perkins (former NIHR Clinician Scientist) is Professor of Critical Care Medicine at the University of Warwick. He is the co-Chief Investigator for the NIHR HTA funded PARAMEDIC trial (a trial of a mechanical chest compression device) and Chief Investigator for the Resuscitation Council (UK) Out of Hospital Cardiac Arrest Registry. He is Chairman of the Resuscitation Council (UK) Advanced Life Support Group, Chair of the European Resuscitation Council CPR/Defibrillation Working Group and Co-Chair of the International Liaison Committee for Resuscitation Basic Life Support Task Force.

Co-investigators

Dr Chris Gale is a NIHR Clinician Scientist and Consultant Cardiologist whose research focus is the use of routine cardiovascular data to inform clinical care. He is a member of the MINAP Academic Group (MAG), National Institute for Cardiovascular Outcomes Research (NICOR) research group, British Cardiovascular Society and Chairs the West Yorkshire Cardiovascular Network Patient and Public Involvement Group. He has published in research journals concerning MINAP data and holds a number of grants concerning MINAP data.

Dr Andrea Marshall is a Senior Research Fellow at the University of Warwick with fifteen years' experience as a statistician and Co-investigator on several research grants. She has specialist expertise into handling missing data and imputation procedures having completed her PhD in this area and published in several research journals.

Dr Peter Kimani is a Research Fellow in Medical Statistics. His research involves developing new statistical methods and analysing trials. He has recently analysed large clinical trials that involved fitting multilevel models.

Prof Tom Quinn is Professor of Clinical Practice and Dean at the University of Surrey. His background is in cardiac nursing, resuscitation and pre-hospital care. He is a member of the MINAP Steering Group, the Joint Royal Colleges Ambulance Liaison Committee and the Nucleus (Steering Group), European Society of Cardiology working group on Acute Cardiac Care. He was previously a member of the DH Heart Policy Team, Heart Disease Task Force and Emergency Cardiac Board and a co-opted member of the Resuscitation Council (UK) Executive. He has published in research journals concerning MINAP data and is PI on a BHF project grant analysing MINAP data in relation to prehospital care.

Prof Iain Squire is a Professor of Cardiovascular Medicine at the University of Leicester. He is a member of the MINAP Academic Group (MAG).

Prof Matthew Cooke is Professor of Clinical Systems Design at Warwick Medical School and Associate Medical Director of Heart of England NHS Foundation Trust. His research focuses on patient safety and clinical systems improvement, particularly in emergency care, as well as involvement in clinical trials in soft tissue injuries and resuscitation. He has a clinical background as consultant in Emergency Medicine. Until recently he was National Clinical Director Urgent and Emergency Care at the Department of Health where he led development of national clinical quality indicators for ambulance services and A&E departments.

Dr John Black is a Consultant in emergency medicine at John Radcliffe Hospital Oxford and Medical Director of South Central Ambulance Service, and is a member of the National Ambulance Medical Directors Group. He Chairs the Intercollegiate Board for Training in Prehospital Emergency Medicine.

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