DEPICT Statistical Analysis Plan

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Version	Date	Reason for modification
1.0	27/03/18	Initial draft circulated to SMG
1.1	16/04/18	Draft amended following comments from the SMG
1.2	10/05/18	Draft amended following comments from the SSC (Approved by SSC 19th June 2018)

1 INTRODUCTION

Study title: Critically ill children and young people: do national Differences in access to Emergency Paediatric Intensive Care and care during Transport affect clinical outcomes and patient experience? The DEPICT study

The structure of the provision of paediatric intensive care has changed in recent years. Prior to 1997, care of critically ill children was undertaken in 28 paediatric intensive care units (PICU), 125 adult intensive care units and 120 children's wards. However, expert opinion suggested centralisation of care and dedicated regional PICUs were set up alongside specialist retrieval team to transport critically ill children from general hospitals to PICUs.

Now, critically ill children can present to any one of 215 hospitals in the UK. Only 25 of these 215 hospitals have an on-site PICU and so children at the other 190 hospitals may need to be transferred to a PICU, at a median distance of 32 km. Transported children represent a third of PICU admissions and the use of a specialist team (paediatric intensive care retrieval team: PICRT) compared to a non-specialist team for inter-hospital transport improves odds of survival by 42%. The majority (~85%) of inter-hospital transfers are performed by specialist paediatric teams. However, we do not know whether differences in timeliness of access to paediatric intensive care and care delivered during stabilisation and transport by specialist teams matter in terms of clinical outcomes.

1.1 STUDY OBJECTIVES

The study objectives of the DEPICT Study are:

Objective 1.1: To perform a quantitative analysis using linked routinely collected audit data to study the association between timeliness of access to paediatric intensive care and clinical outcomes in a national cohort of critically ill children transported to PICU. [Timeliness of access to intensive care will be measured by time to arrival at bedside after acceptance; time of referral to time of acceptance; time of referral to time of admission to PICU]

Objective 1.2: To perform a quantitative analysis using linked routinely collected audit data to study the association between care delivered by PICRTs and clinical outcomes in a national cohort of critically ill children transported to PICU. [We will study specific aspects of PICRT care such as team composition, interventions performed and critical incidents during transport].

Objective 1.3a: To explore, using qualitative methods (individual interviews and workshops) and questionnaires, the experiences and perspectives of a purposively sampled national cohort of parents of transported critically ill children.

Objective 1.3b: If and where feasible, to use innovative methods to explore the experiences of transported critically ill children.

Objective 1.4: To explore, using qualitative methods (individual interviews and workshops), the experiences and perspectives of a purposively sampled national cohort of clinicians from a range of settings (acute general hospitals, PICRTs and PICUs) and service managers/NHS commissioners.

Objective 2.1: To perform cost effectiveness analyses of PICRT provision for critically ill children, comparing different service models currently in use.

Objective 2.2: To use mathematical modelling and location allocation optimisation methods to explore whether alternative models of service delivery for PICU/PICRT services can improve clinical outcomes while remaining cost effective.

Objective 2.3: To synthesise study findings to inform the development of evidence-based national standards of care and information resources for families and clinicians.

1.2 STUDY DESIGN

Mixed methods study including a) retrospective quantitative analysis of linked routinely collected PICANet audit data, b) prospective qualitative study involving questionnaires and interviews of critically ill children transported to intensive care and their families, clinicians and managers, c) health economic analysis and d) mathematical modelling to evaluate whether alternative models of service delivery can improve clinical and cost effectiveness.

This statistical analysis plan relates to Objectives 1.1 and 1.2, which form the quantitative workstream.

2 APPROVALS

This table describes the required approvals for the DEPICT Study and provides the physical location for the evidence of it on the University of Leicester servers.

Approval required	**Obtained?**
Data access and transfer approval from PICANet	Done
Fair processing notice for PICANet	Done
Fair processing notice for ICNARC	Done
Data access and transfer approval from ICNARC	Done
CAG approval for Section 251	Done
REC approval	Done
NIHR contract	
Study protocol	
NHS Digital application	Done

NHS Wales Data Request	In progress	[redacted]

3 DATA SOURCES

3.1 PAEDIATRIC INTENSIVE CARE AUDIT (PICANET) TRANSPORT, RETRIEVAL AND ADMISSIONS

The Paediatric Intensive Care Audit Network (PICANet) has collected data on all admissions to paediatric intensive care in England and Wales since 2003. Data collection was extended to Scotland (2004: Edinburgh and 2007: Glasgow), Northern Ireland (2008: Belfast) and the private English units (2010: Harley St, 2013: Portland). The DEPICT Study focusses on care in England and Wales.

Specialist paediatric transport has existed in different forms for several years, and PICANet data collection related to transport and retrieval began in 2012. Services have moved towards specialist centralised transport teams over time since then (see table), with some areas retaining unit based transport teams for longer than others. All transport services, whether unit-based or centralised, began submitting data to PICANet in 2012. Data schemas for PICANet can be found at: R:\DEPICT\Shared\Data\Schemas

Transport service	**Date of first event reported to PICANet**
Children's Acute Transport Service (CATS)	1/1/2012 (referral) 1/1/2012 (transport)
Children's Medical Emergency Transport Service (COMET)	15/3/2017 (referral) 15/3/2017 (transport)
Embrace	27/12/2011 (referral) 27/12/2011 (transport)
KIDS Intensive care and Decision Support	14/10/2014 (referral) 16/03/2000 (transport)
North East Children's Transport and Retrieval Service (NECTAR)	20/08/2014 (referral) 02/08/2015 (transport)
North West and North Wales (NWTS)	01/01/2012 (referral) 17/01/2002 (transport)
Southampton and Oxford (SORT)	01/12/2012 (referral) 02/12/2012 (transport)
South Thames Retrieval Service (STRS)	01/01/2013 (referral) 01/01/2013 (transport)
Wales and West Acute Transport for Children (WATCh)	01/04/2014 (referral) 03/09/2015 (transport)

3.2 INTENSIVE CARE NATIONAL AUDIT AND RESEARCH (ICNARC)

Information from ICNARC will be provided on children who are admitted to adult intensive care units to receive care. The data request from ICNARC is for the following data items:

Unique CMP identifier (pseudoanonymised), NHS number (to allow the linkage, not to be provided to the research team), date of birth, sex, residential postcode (or IMD score), admitting unit, date of admission, source of admission, ICNARC physiology score, PRISM

score, date of discharge (or length of stay), vital status at discharge, discharge location, type and duration of organ support interventions provided (respiratory, cardiovascular, renal, neurological), location prior to admission.

Identifiable PICANet and ICNARC data including NHS number will be passed from the University of Leeds and ICNARC to NHS Digital to allow for linkage with ONS and HES data (see below). The data flow is described in the diagram.

3.3 DATA LINKAGE

The ICNARC and PICANet data sources will be linked with the following data sources:

Office of National Statistics (ONS): linkage undertaken by NHS Digital

Information extracted from death certificates will be provided by ONS.

As of May 2018 it is unclear if we will be able to obtain full ONS data and if not we will request derived information about 30-day, 90-day and 1-year mortality post-admission.

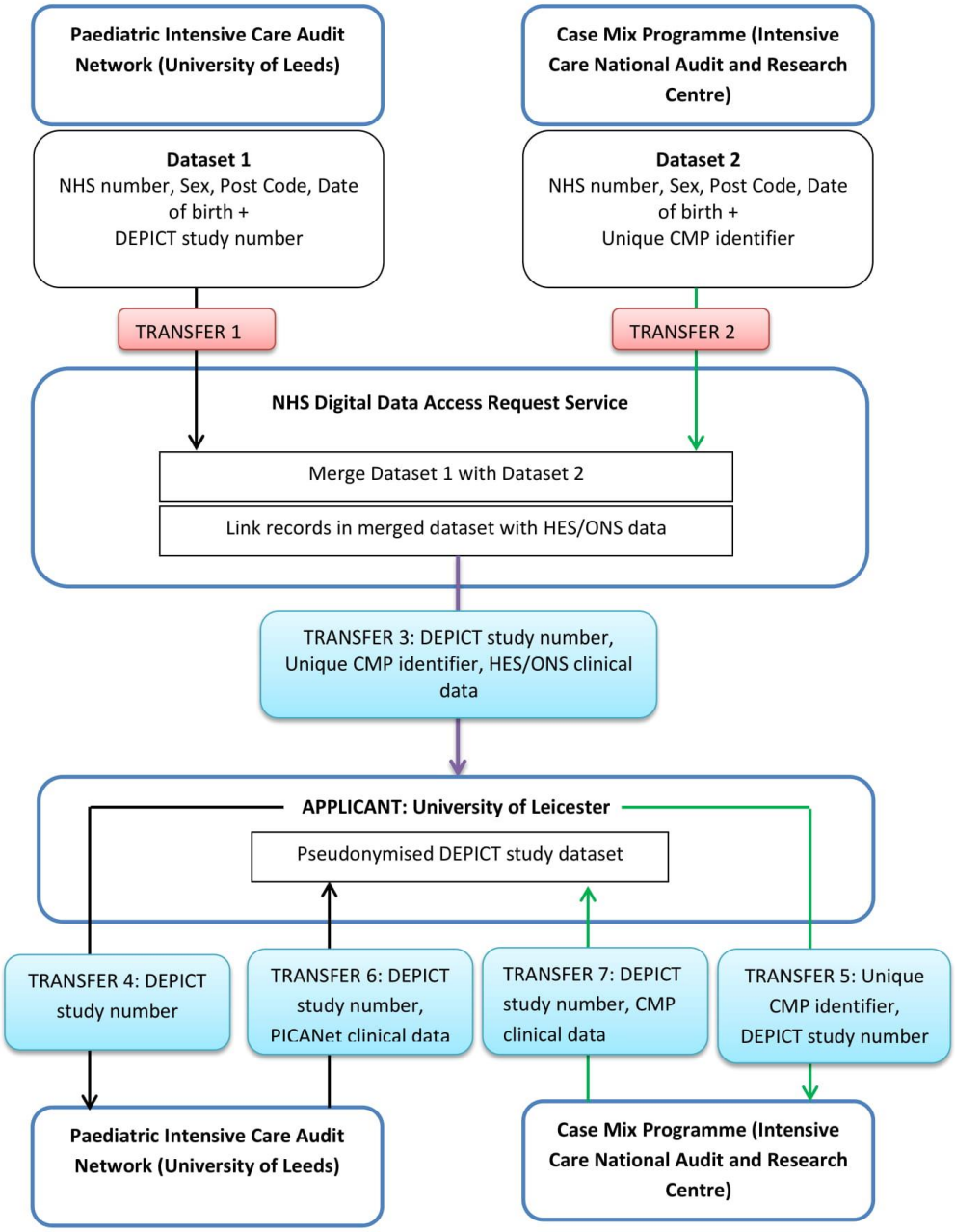
Hospital Episodes Statistics (HES): linkage undertaken by NHS Digital

Information from HES will be used to provide information about admissions via Accident & Emergency and to receive information about hospital care received in a non-paediatric intensive care environment (e.g. on a ward). This can be used to inform information about length of stay in other hospital environments; re-admission to hospital or other emergency care received.

Admitted Patient Care (APC) and Emergency Department Dataset (EDDS), NHS Wales: linkage undertaken by NHS Wales Informatics Service

The ethical approval and CAG approval to access the Welsh data have not yet been acquired (as at May 2018). When these have been obtained, data will be applied for. NHS Wales will only undertake linkage using NHS Number.

FLOW OF DATA IN THE DATA LINKAGE PART OF THE DEPICT STUDY



The DEPICT study, IRAS ID 218569 07/07/2017

Red boxes indicate transfers where personal data will be included; blue boxes indicate no personal data will be included in the transfer. All transfers will utilise secure transmission means.

4 DATA & DATA MANIPULATION

The data acquisition will follow these steps as outlined in the NHS Digital application:

1) Data flows to NHS Digital from the University of Leeds (PICANet) and ICNARC (Case Mix Programme) will each securely transfer a file to the NHS Digital Data Access Request Service (DARS). These files will contain person-identifiable information (NHS Number, sex, post code, date of birth) and unique study identifiers (PICANet: DEPICT Study Number; CMP: CMP identifier) required to perform the data linkage.
2) NHS Digital will identify common records between PICANet data and CMP data.
3) Data flow from NHS Digital will return linked HES and ONS mortality data for all individuals in the PICANet or ICNARC datasets to the University of Leicester - NHS Digital will supply a list of the study identifiers common to PICANet and CMP to University of Leicester - The unique study identifiers (DEPICT study number and CMP identifier) will be appended to the end of every episode record returned to the University of Leicester.
4) The team at the University of Leicester will securely transfer the list of DEPICT study numbers and CMP study identifiers to University of Leeds and ICNARC respectively. No HES or ONS data or personal identifiers will be transferred.
5) Data flow from University of Leeds (PICANet) and ICNARC (CMP) University of Leeds and ICNARC will provide admission level clinical data from their respective audits for the specific DEPICT and CMP identifiers to University of Leicester by means of secure transfer. No personal identifiers will be transferred.

Data acquisition from NHS Wales will follow a similar process and data flow.

4.1 INCLUSION/EXCLUSION

Data on all children (≤16 years old) admitted to PICUs in the England and Wales from 2014 to 2016 following transport by a specialist team will be included. Transport events will be linked with the appropriate admission information and other longer-term outcome data. Some children will be transported and admitted more than once over this time period. Summary statistics will be produced for both admission and for the individual child, and analyses will be undertaken using both approaches and compared. For the analysis at child level, the admission closest to the final event will be used and a variable will be included to indicate if they had previous admissions to PICU.

Exclusions will be made for:

- Transport of adults (age >16 years)
- Transport to an unknown location; no match between transport and admission event; transport performed by non-specialist team; transport performed by neonatal team.

4.2 SAMPLE SIZE

PICANet data from 2014/15 indicates that the 30-day mortality rate for transported PICU admissions is approximately 7% and that transport teams reach critically ill children within 3 hours of referral acceptance in 85% of cases (the current target). We anticipate a sample of

15,000 transports over the three year time window of the DEPICT Study. Of the 15,000 transports we anticipate that approximately 12,750 (85%) will be made in less than 3 hours. The remaining 2,250 (15%) will be made in more than 3 hours. We have adequate power to detect a 3 percentage point reduction in mortality (7% to 4%). This sample is assuming that each transport and admission is a separate child, when in reality a single child may contribute multiple transports.

Adjustments will be made using the 'rule of thumb' of at least ten events per adjustment. For example, if we observed 400 deaths, we would make no more than 40 adjustments. However, we will work to ensure statistical parsimony by keeping the model as simple as practical.

5 ANALYSIS

5.1 MISSING OR IMPLAUSIBLE DATA

Data quality and completeness of the PICANet data is high. Validation visits are undertaken to each unit or transport service approximately every 18 months to inspect data quality of entries in the preceding months. However, data checks on all data will still be completed to investigate for missing or implausible data values.

According to correspondence with ICNARC, data quality of the ICNARC data is believed to be reasonable for the variables requested. The only issue reported at this stage is that certain aspects of the PRISM (paediatric risk of mortality score) score are not collected. The data items and whether they are collected (collected: yes/no) are as follows: SBP (yes); DBP (yes); heart rate (yes); respiratory rate (yes); P/F (yes); PaCO2 (yes); PT/PTT (no); Bilirubin (no); Calcium (no); Potassium (yes); Glucose (yes); Bicarbonate (yes); Pupils (reactivity not size); GCS (yes, if not sedated).

If levels of missing data are high (≥10%) for key variables, reasons for this will be investigated (e.g. whether one particular transport team has a certain variable consistently missing – indicating this is not missing at random) and methods to account for this may be used. For example, if we believe that missing PIM scores are probably those of the sickest children, we may propose to undertake a sensitivity analysis to impute poor scores and rerun the initial analyses to assess the impact on the results. Conversely, if we believe data are missing at random we will investigate whether multiple imputation may be appropriate. At this stage we are unaware of the level of missing data which will be encountered. We will develop robust proposals for handling each variable as we become aware of the level of missingness and present these to the Study Management Group for approval before analysis is conducted.

5.2 SUMMARY STATISTICS

Summary statistics will be presented to describe the population including:

- Number of children transferred, n (%)

- Age, mean (SD) and sex, n (%) of transported children
- Characteristics of the transports undertaken, n (%)
    - E.g. grade of team leader; care area of handover; operational times (median, range); interventions prior to or during transport, n (%)
- Interventions during or prior to transport conducted by the retrieval team, n (%)
    - E.g. intubation; CVC insertion; primary intraosseous access; arterial access; inotrope infusion; chest drain; ECMO; adverse events en route.
- Primary diagnosis reason, n (%)
    - E.g. respiratory; neurological; cardiovascular; infection; endocrine/metabolic; haematology/oncology; trauma; other
- Reason for admission, n (%)
    - E.g. bronchiolitis; seizure disorder; asthma; croup; postoperative; diabetic ketoacidosis
- PIM-2/PIM-3 predicted mortality risk, median and range
- PIM-2/PIM-3 predicted mortality risk categorised, n (%):
    - Grouped as <1; 1 to <5; 5 to <15; 15 to <30; 30-100.
- PaO_2/FIO_2 ratio, n (%)
    - Grouped as: <200; 201-300; >300
- Cardiac arrest before contact with transport team, n (%)
- Died in PICU; died within 30 days of admission to PICU; died within 90 days of admission; died within one year, n (%)
- Length of PICU stay, median numbers of days and range
- Information about daily interventions in the PICU, median days (range)

Whilst they will not form part of the main analysis, we will also report the number of children who die en route, and the median (range) time taken to reach their bedside by the transport team.

The differences between the transport teams in terms of their team composition, demographics they serve and facilities they have available will be described descriptively if possible.

5.3 FORMAL STATISTICAL ANALYSES

5.3.1 Outcomes for all analyses

Primary outcome:

30-day mortality following PICU admission (following first admission) using data from the Office of National Statistics.

Secondary outcomes to include:

a) Mortality at fixed time-points (PICU discharge, 90 days and 1 year following [first] PICU admission – data linked from ONS)

b) Number of PICU admissions during study period and time to readmission (if applicable)

c) Length of stay in PICU (number of days from PICU admission to discharge, for each PICU admission)

d) Resource use in PICU (number of days of invasive ventilation, vasoactive agent therapy, renal replacement therapy and extra-corporeal life support during PICU stay, for each PICU admission)

e) Length of hospital stay linked to the first PICU admission (number of days from hospital admission to hospital discharge)

f) Number of A&E attendances in the 12 months following discharge from the first PICU admission (using data from HES and NHS Wales)

g) Hospital resource use (total number of days admitted to hospital) in the 12 months following discharge from the first PICU admission (using data from HES and NHS Wales)

5.3.2 Model development

Model development will follow these steps:

1. Selection of key confounders to be included in analyses. Potential confounders and adjustments are included in the below table. Discussion will be led by clinical colleagues and facilitated by the statistician who will provide information about data available via the linked datasets and also provide details about data quality and potential issues with the data (see Section 5.1).
2. Directed Acyclic Graphs (DAG) will be produced following discussions to visually represent the potential adjustments for each model. The DAG will be approved by clinical colleagues involved in this study. This discussion will initially focus on Model 1 with the key outcome of 30-day mortality.
3. Formal model will then be fitted (see Section **Error! Reference source not found.**)
4. Model checking will be conducted (see Section 5.3.4)
5. Sensitivity analyses on assumptions and robustness of results will be conducted (see Section 5.3.5).

The DAG developed for each research question will be approved by the Study Management Group before analysis begins and it will be published in any paper presenting the results. Each model will have a different DAG. Use of a DAG will allow us to minimise the number of adjustments required. DAGitty (http://www.dagitty.net/) will be used to facilitate the drawing of the DAG and selecting the minimal model required.

Potential variables for inclusion in analyses

For our first model which will investigate the issues of timeliness of access to care, there are three time scales which can be defined as 'timeliness' (our exposure of interest):

- Time to arrival at bedside after acceptance (we will investigate this first)
- Time of referral to time of acceptance
- Time of referral to time of admission to PICU

For each of these time scales there are different factors which will be important. For example, care provided by the retrieval team upon arrival will impact on the time to

admission in the PICU but not the other time scales. This table provides a pool of variables which we will select from.

List of potential confounders for consideration in each of the models.

Variable	Data source
Age	PICANet & CMP
Sex	PICANet & CMP
Ethnicity	HES
Pre-existing comorbidities (or a proxy, e.g. time in hospital in the previous year)	HES, PICANet & CMP
Deprivation (IMD score)	PICANet & CMP (via postcodes)
Diagnosis	PICANet/CMP/HES
Severity of illness (PIM-2/PIM-3 score and individual variables from first contact with transport team, not from referral)	PICANet
Ventilated at referral	PICANet
Previous admission to intensive care	PICANet/CMP
Volume of referring hospital	HES or RCPCH data
Interventions prior to arrival of the transport team	PICANet
Referral location (A&E, HDU, theatre, ward etc.)	PICANet
Distance from transport team to referring hospital	PICANet
Season (winter defined as Nov to Feb)	PICANet/CMP
In hours versus out of hours (to include evenings and weekends)	PICANet
Interventions conducted when retrieval team arrives	PICANet
Grade of team leader	PICANet

The second model which will investigate the care delivered en route by the transport team will select variables from the above table as appropriate.

5.3.3 Statistical methods

Primary outcome

Two main models will form the basis of the analysis, both initially using the primary outcome of mortality.

Model 1: The impact on mortality due to timeliness of access to care in transported children

Three time frames will be considered when investigating the outcome of mortality and timeliness of access to care:

- Time to arrival at bedside after acceptance (we will investigate this first)

- Time of referral to time of acceptance
- Time of referral to time of admission to PICU

A variable to represent timeliness of access to care will be included to indicate if the transport was made in the desired time frame (e.g. continuous time to arrival or dichotomised using any targets: <3 hours: yes/no) or in groupings of 30 mins (0-30 mins; 30-60 mins; 60-90 mins etc.). Other confounders will be identified and included (see Section 5.3.2). If reasons for delay want to be investigated then the PICANet free text comments fields will be interrogated.

Differences which may exist between the transport teams will be accounted for in all analyses of the primary outcome either via use of logistic mixed models (random effect term for transport team) or logistic models with robust standard errors to account for clustering within transport services. Both of these approaches will give very similar (although not identical) results in terms of the coefficients. The model fit will be assessed to see if consideration of transport team improves the model fit via use of the AIC. If differences between transport teams are of direct interest, a categorical term to indicate the transport team will also be included within the model.

Model 2: Care delivered by the transport team en route to PICU and the impact on mortality

Three aspects of care delivered by the PICRT will be studied with regards to the primary outcome of mortality:

a) Team composition: grade of PICRT team leader (consultant, junior doctor, advanced nurse practitioner); seniority of transport nurse; presence of medical technician on transport

b) Interventions performed by the transport team (airway-related: intubation, reintubation; vascular access: central venous, arterial, intraosseous; chest drain; use of vasoactive agents; non-invasive ventilation)

c) Occurrence of a critical incident during transport

This will be analysed in the same approach as Model 1, via use of logistic models or logistic mixed models.

Secondary outcomes

The analyses for Model 1 and 2 will be repeated for the secondary outcomes. Confounders and adjustments will again be considered for their appropriateness and then the following methods will be used as an initial basis:

- Length of stay (PICU, hospital): survival analysis approaches including competing risks
- Resource use in PICU and hospital resource use following PICU discharge: Negative binomial regression models (to account for the fact that many children will have no resource use for certain interventions)

- A&E attendances: logistic regression (ever re-admitted to A&E: yes/no); number of re-admissions (Poisson or negative binomial regression)

Approach to modelling covariates

The most appropriate approach for modelling covariates will be discussed clinically, and also investigated statistically. Splines and fractional polynomials will be considered for continuous variables and if their use reduces the AIC substantially then these will be used. However, this will be considered alongside the issues of whether the odds ratios or equivalent remains interpretable.

Similarly, interactions if thought to be clinically relevant will be included. The most important interaction is likely to be between age and diagnosis but all interactions between age, sex, diagnosis and size of referring hospital (and any other key variables identified by our clinical colleagues) will be considered.

5.3.4 Model checking

Model checking will be undertaken as appropriate for the method selected, to ensure over- or under- fitting has not occurred) but will include: Hosmer Lemeshow test; AUC (c-statistic); Farrington statistic; cross validation and Briers score for the primary outcome which will utilise logistic regression. Stability of model estimates will be assessed via bootstrapping.

5.3.5 Sensitivity analyses

All analyses undertaken will be assessed for their robustness via a thorough sensitivity analysis. These will fall under three types:

1. The impact of unobserved confounding will be investigated using instrumental variables (see below)
2. Assumptions surrounding missing data
3. Assumptions of statistical models

Potential instrumental variables

Instrumental variables can be used to investigate the impact of unmeasured confounding and an instrumental variable is one which:

1. Must not be correlated with the outcome (mortality) other than through the exposure (e.g. time to reach bedside)
2. Must be highly predictive of the exposure (e.g. time to reach bedside)
3. The relationship between the instrumental variable and the exposure must not be confounded.

The two candidate variables for the instrumental variable are:

- Distance from centralised transport team to the referring hospital.
- Activity level of the transport service at the time of the referral (a measure of how busy the service is, e.g. number of transports in the surrounding 24 hours).

5.3.6 Reporting conventions

Output

(Adjusted) odds ratios will be reported to 1 decimal point with 95% confidence intervals. Predicted probabilities will also be provided for selected groups of characteristics. When possible, graphical approaches or diagrams will be used to facilitate the understanding and interpretation of results.

Significance levels

P-values will not be presented and instead 95% confidence intervals will be given.

Small number suppression

Small numbers will be suppressed in line with HES Guidance, but broadly:

- Totals less than 5 will generally not be presented at postcode, LSOA, GP and lower levels.
- Totals less than 5 will be presented if at national or regional level. Therefore transport services with numbers of deaths less than five would be reported as these operate at regional level.
- Certain sensitive diagnoses or conditions will be suppressed (in line with clinical advice).
- Number of deaths will not be suppressed.