UCL INSTITUTE OF CHILD HEALTH

Great Ormond Street Hospital for Children NHS Foundation Trust

Joint Research and Development Office
Division of Research and Innovation

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

Protocol Number: 15HC47
Protocol Version: Version 3.2
Short title or acronym: The DEPICT study

Chief Investigator: Dr Padmanabhan Ramnarayan
Consultant in Paediatric Intensive Care and Retrieval
Children's Acute Transport Service (CATS)
Great Ormond Street Hospital NHS Foundation Trust
26-27 Boswell Street, London, WC1N 3JZ

Investigators:
Professor Elizabeth Draper, University of Leicester
Dr Jo Wray, Great Ormond Street Hospital
Professor Steve Morris, University College London
Dr Christina Pagel, University College London
Dr Will Marriage, University Hospitals of Bristol
Dr Fatemah Rajah, Sheffield Children's Hospital
Dr Patrick Davies, Nottingham University Hospital
Ms Eithne Polke, Great Ormond Street Hospital
Mr Paul Mouncey, Intensive Care National Audit and Research Centre
Ms Rachel Lundy, NHS England
Matthew Entwistle and Anna Pearce, Parent Representatives

Funder: National Institute of Health Research Health Services Delivery Research (NIHR HSDR)

The investigators have no potential conflicts of interest.

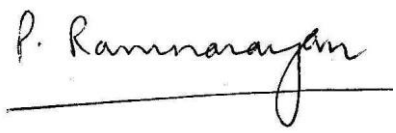
Sponsor

Great Ormond Street Hospital for Children NHS Foundation Trust
Joint R&D Office GOSH/ICH based at UCL Institute of Child Health
30 Guilford Street
London WC1N 1EH
United Kingdom
Email: Research.Governance@gosh.nhs.uk

Signatures

The Chief Investigator, Principal Investigators and Sponsor have discussed this protocol. All have agreed to perform the investigation as written and to abide by this protocol except in case of medical emergency or where departures from it are mutually agreed in writing.

Chief Investigator



Signature

Date: 11th December 2018

Participating Sites and Local Principal Investigators (PI)

PICU sites

1	Dr Padmanabhan Ramnarayan Children's Acute Transport Service (CATS) Great Ormond Street Hospital NHS Foundation Trust 26-27 Boswell Street, London, WC1N 3JZ Email: p.ramnarayan@gosh.nhs.uk	2	Dr Sanjay Revanna KIDS Intensive Care and Decision Support Birmingham Children's Hospital NHS Foundation Trust Steelhouse Lane, Birmingham, B4 6NH Email: sanjay.revanna@bch.nhs.uk
3	Dr Benedict Griffiths South Thames Retrieval Service (STRS) Evelina Children's Hospital, Guy's and St Thomas' NHS Foundation Trust Westminster Bridge Rd, Lambeth, London SE1 7EH Email: BenedictThomas.Griffiths@gstt.nhs.uk	4	Dr Dorthe Grainger North West / North Wales Transport Service Central Manchester University Hospitals NHS Foundation Trust Upper Brook Street, Manchester, M13 9WL Email: dorthe.grainger@cmft.nhs.uk
5	Dr Fatemah Rajah EMBRACE transport service Sheffield Children's NHS Foundation Trust Western Bank, Sheffield S10 2TH Email: fatemah.rajah@sch.nhs.uk	6	Dr Peter Davis University Hospitals of Bristol NHS Foundation Trust Upper Maudlin Street, Bristol, BS2 8BJ Email: peter.davis@uhbristol.nhs.uk
7	Dr Aravind Kashyap North East Children's Transport and Retrieval (NECTAR) The Newcastle upon Tyne Hospitals NHS Foundation Trust Freeman Road, High Heaton, Newcastle upon Tyne, NE7 7DN Email: aravind.kashyap@nuth.nhs.uk	8	Dr Patrick Davies Paediatric Intensive Care Unit, Nottingham Children's Hospital Nottingham University Hospitals NHS Trust Derby Road, Nottingham, NG7 2UH Email: patrick.davies@nuh.nhs.uk
9	Dr Peter Barry Department of Child Health Level 5, Robert Kilpatrick Clinical Sciences Building Leicester Royal Infirmary, Leicester, LE2 7LX Email: pwb1@leicester.ac.uk	10	Dr Gareth Jones Southampton and Oxford Retrieval Team (SORT) University Hospital Southampton NHS Foundation Trust Tremona Road, Southampton, SO16 6YD Email: gareth.jones@uhs.nhs.uk
11	Dr David Inwald Paediatric Intensive Care Unit, St Mary's Hospital Imperial College Healthcare NHS Trust Praed Street, London, W2 1NY Email: d.inwald@imperial.nhs.uk	12	Dr Akash Deep Paediatric Intensive Care Unit, King's College Hospital King's College Hospital NHS Foundation Trust Denmark Hill, London, SE5 9RS Email: akash.deep@nhs.net
13	Dr Nazima Pathan	14	Dr Angela Aramburo

	Department of Paediatrics, University of Cambridge Paediatric Intensive Care Unit, Addenbrookes Hospital Hills Road, Cambridge, CB2 0QQ Email: np409@cam.ac.uk		Paediatric Intensive Care Unit, Royal Brompton Hospital Royal Brompton and Harefield NHS Foundation Trust Sydney St, Chelsea, London SW3 6NP Email: a.aramburo@rbht.nhs.uk
15	Dr Nayan Shetty Paediatric Intensive Care Unit, Alder Hey Children's Hospital Alder Hey Children's NHS Foundation Trust Eaton Road, Liverpool L12 2AP Email: nayan.shetty@alderhey.nhs.uk	16	Dr John Alexander Paediatric Intensive Care Unit, Royal Stoke University Hospital University Hospitals of North Midlands NHS Trust Newcastle Road, Stoke-on-Trent, ST4 6QG Email: john.alexander@uhnm.nhs.uk
17	Dr Joanne Lumsden Paediatric Intensive Care Unit, Leeds Children's Hospital The Leeds Teaching Hospitals NHS Trust Clarendon Wing, Leeds General Infirmary, Leeds, LS1 3EX Email: jolumsden@nhs.net	18	Dr Nicholas Prince Paediatric Intensive Care Unit, St George's Hospital St George's University Hospital NHS Foundation Trust Blackshaw Road, Tooting, London, SW17 0QT Email: Nprince@nhs.net
19	Dr Naomi Edmonds Paediatric Critical Care Unit, Royal London Hospital Barts Health NHS Trust Turner St, Whitechapel, London E1 1BB Email: naomi.edmonds@bartshealth.nhs.uk	20	Dr Avishay Sarfatti Paediatric Intensive Care Unit, Oxford Children's Hospital Oxford University Hospitals NHS Foundation Trust Headley Way, Headington, Oxford OX3 9DU Email: Avishay.Sarfatti@ouh.nhs.uk
21	Dr Siva Oruganti Paediatric Intensive Care Unit, Noah's Ark Children's Hospital for Wales University Hospital of Wales, Cardiff and Vale University Health Board Heath Park, Cardiff, CF14 4XW Email: siva.oruganti@wales.nhs.uk		

DGH sites

1	Dr Sanjay Rawal Basildon University Hospital Nethermayne Basildon Essex SS16 5NL Email: Sanjay.Rawal@btuh.nhs.uk	2	Dr Susie Holt Countess of Chester Hospital NHS Foundation Trust Countess of Chester Health Park Liverpool Road Chester, CH2 1ULEmail: Susieholt@nhs.net

3 Dr Youssef Abourahma
Aneurin Bevan University Health Board
Royal Gwent Hospital
Cardiff Road
Newport
NP20 2UB
Email: Youssef.Abourahma@wales.nhs.uk

4 Dr Katherine Deakin
Pinderfields Hospital
Aberford Road
Wakefield
WF1 4DG
Email: Kathryn.Deakin@midyorks.nhs.uk

5 Dr Mariam Rice
St. Mary's Hospital,
Parkhurst Road,
Newport,
Isle of Wight,
PO30 5TG
Email: Mariam.Rice@iow.nhs.uk

6 Dr David Broodbank
United Lincolnshire Hospitals NHS Trust
Hospital sites:
Pilgrim Hospital Boston,
Sibsey Road,
Boston,
Lincolnshire
PE21 9QS
&
Lincoln County Hospital,
Greetwell Road,
Lincoln,
Lincolnshire,
LN2 5QY

Email: Dr David.Broodbank@ULH.nhs.uk

7 Dr Julian Berry
Royal Cornwall Hospitals NHS Trust
Treliske, Truro, Cornwall,
TR1 3LJ
Email: Julian.Berry@rcht.cornwall.nhs.uk

1 AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1	2	20 Nov 2017	P Ramnarayan	1. Updated PI details for Cardiff and Vale University Health Board (Wales site) 2. Updated PI details for Oxford University Hospital NHS Trust. 3. Clarification of the inclusion criterion for the qualitative and questionnaire study: transports performed by PICRTs as well as other teams will be eligible (Section 8.2.1). 4. Inclusion of a new section covering consent processes for parents whose children died on the intensive care unit prior to being approached for participation in the study (Section 8.2.1.1). 5. Addition of a paragraph to clarify that both parents will be able to complete transport questionnaires separately if they wished to do so (Section 8.2.2). 6. Clarification regarding the timing of approach for consent: timing is now left to the discretion of the clinical team (Section 9).
2	2.1	27 Mar 2018	P Ramnarayan	Updated PI details for University Hospital Bristol NHS Trust.
3	3	28 Aug 2018	P Ramnarayan	1. Details of data linkage for Welsh NHS data added to page 18 and 19, Section 8.1.2.2 2. Change in time frame for parents to decide to participate in feedback study (work stream B), page 34, Section 9.
4	3.1	19 Nov	P Ramnarayan	1. Added 4 DGH sites to the list of

		2018		participating sites
5	3.2	11th Dec 2018	P Ramnarayan	1. Added a further 3 DGH sites to the list of participating sites

2 ABBREVIATIONS

CATS	Children's Acute Transport Service
CI	Chief Investigator
CRF	Case Report Form
GCP	Good Clinical Practice
GOSH	Great Ormond Street Hospital
GP	General Practitioner
ICF	Informed Consent Form
ISF	Investigator Site File
ICH	International Conference of Harmonisation
NHS	National Health Service
NRES	National Research Ethics Service
PI	Principal Investigator
PIL	Participant/ Patient Information Leaflet
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
SAE	Serious Adverse Event
SDV	Source Data Verification
SOP	Standard Operating Procedure
TMF	Trial Master File
UCL	University College London

3 STUDY SYNOPSIS

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
Sponsor name	Great Ormond Street Hospital NHS Foundation Trust
Primary objective	To study how clinical outcomes of critically ill children transported to paediatric intensive care (PIC) are affected by national variations in timeliness of access to paediatric intensive care.
Secondary objective (s)	1. To study how the experience of critically ill children (and their families) transported to paediatric intensive care are affected by national variations in timeliness of access to paediatric intensive care. 2. To study how clinical outcomes of critically ill children transported to paediatric intensive care are affected by national variations in care provided by PIC retrieval teams (PICRT) during stabilisation and transport. 3. To study how the experience of critically ill children (and their families) transported to paediatric intensive care are affected by national variations in care provided by PIC retrieval teams (PICRT) during stabilisation and transport. 4. To study the relative cost effectiveness of current PICRTs. 5. To use mathematical modelling to evaluate whether alternative models of PICRT service delivery can improve clinical and cost effectiveness.
Study Design	Mixed methods study including a) quantitative analysis of linked routinely collected PICANet audit data, b) 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.
Study Endpoints	Primary outcome: 30-day mortality Secondary outcomes: Mortality in PICU, at 90 days and within the first year after the index PICU admission; length of stay in PICU; Resource use in PICU (days on invasive ventilation, vasoactive agent therapy, renal replacement therapy and extra-corporeal life support); length of hospital stay for the index admission; number of hospital admissions and days in hospital in the 12 months following the index PICU admission.
Sample Size	Quantitative analysis: PICANet data analysis on 15,000 transports performed by PIC retrieval teams. Questionnaires: 800-1000 completed transport questionnaires. Interviews: 50 parents of critically ill children transported to PICU; 20-30 critically ill children transported to PICU; 35-40 clinicians involved in the care

	of critically ill children; 4-8 service managers/NHS commissioners.
Summary of eligibility criteria	Children and young people (age <16 years) transported by a PIC retrieval team for emergency admission to a paediatric intensive care unit in England and Wales.
Intervention	None
Procedures: Screening & enrolment	Only the qualitative study will involve prospective patient recruitment. For this part of the study, all emergency admissions to participating PICUs over a 12-month period will be screened for eligibility. Eligible patients will be identified and consent sought for participation in the study.
Baseline	Consent will be sought from parents/legal guardians for completion of transport questionnaires; for potential contact with the researchers for participation in an interview at a later date; and for future contact by a researcher to administer quality of life questionnaires at 12 months.
Treatment period	Over a 12-month period, using questionnaires, we will gather feedback from parents regarding the transport of their children. We will conduct semi-structured interviews of parents to elicit their experiences and perceptions regarding emergency transport to PICU (where possible, the experiences of children themselves), 35-40 clinicians working in acute general hospitals/PICUs/PICRTs, and service managers/commissioners.
End of Study	We will collect follow up data at 12 months from parents/families regarding the child's quality of life using validated questionnaires.

Table of Contents

4 INTRODUCTION

4.1 Background

The United Kingdom (UK) has one of the highest child mortality rates in Europe.[1] In recent years, two confidential enquiries and one Royal College report related to preventable child deaths have highlighted how deficiencies in the organisation and delivery of acute care may result in poor clinical outcomes, and how improvements in the recognition and management of acutely ill children may lead to better clinical outcomes.[2, 3]

4.1.1 CENTRALISATION OF PAEDIATRIC INTENSIVE CARE

Over the past few decades, evidence linking higher volume to better outcomes has led to the centralisation of specialist services such as cancer surgery, perinatal care and trauma.[4-6] Through concentration of skills in fewer centres, centralisation is believed to improve clinical outcomes and enable cost-effective delivery of specialist care. However, conversely, the need for patients to travel increased distances to access acute services may compromise clinical outcomes.

Prior to 1997, the care of critically ill or injured children (defined as anyone under the age of 16) in the UK was fragmented: intensive care was delivered in 28 PICUs (mean: 233 admissions/year), 125 adult intensive care units (mean: 21 admissions/year) and 120 children's wards (mean: 31 admissions/year).[7] In 1997, based on expert opinion and scientific evidence, the UK Department of Health recommended that paediatric intensive care (PIC) services should be centralised.[8] Dedicated regional PIC units (PICUs) were established, and specialist PIC retrieval teams (PICRTs) were set up to transport critically ill children from general hospitals to PICUs. PICRTs act as mobile intensive care teams: they travel to general hospitals and start paediatric intensive care, ensuring that specialist expertise is not delayed until the patient reaches the PICU, and safely transport critically ill children to the PICU.[9]

Currently, although children may first present when they are critically ill to one of 215 acute hospitals in the UK, only 25 have a PICU; children presenting to other general hospitals require to be transferred to a hospital with a PICU, located a median distance of 32 km away (IQR 14-57).[10] Our research has previously shown that the use of PICRTs (rather than non-specialist teams) for the inter-hospital transport of critically ill children improves the odds of their survival by 42%.[10] The majority (~85%) of inter-hospital transports of critically ill children in the UK are currently performed by PICRTs.[11]

4.1.2 VARIATIONS IN ACCESS TO PAEDIATRIC INTENSIVE CARE AND CARE DELIVERED BY PICRTS

Each year, nearly 5000 critically ill children are transported by PICRTs from general hospitals to UK PICUs. National audit data from the Paediatric Intensive Care Audit Network (PICANet) reveal wide variations in the timeliness of access to paediatric intensive care in these patients.[11] Firstly, the

median time taken for PICRTs to reach critically ill children at general hospitals ranges from 1 to 4 hours, reflecting considerable differences in how soon a critically ill child can expect to start receiving paediatric intensive care. During the winter surge period, some children may even wait up to 12-24 hours for the PICRT to arrive. Secondly, there is variation in the time taken by PICRTs to transport children into the admitting PICU, reflecting differences in how soon a critically ill child can start receiving definitive care (e.g. surgery) only available in a specialist centre.

Similarly, PICANet data indicate that there is considerable variation in the care provided to critically ill children by PICRTs prior to PICU admission, in terms of the seniority of the transport team leader (consultant, junior doctor, or advanced nurse practitioner), critical care interventions performed by the transport team (e.g. intubation or central venous catheterisation and delivery of vasoactive drug infusions), and the frequency of critical incidents (e.g. accidental extubation) occurring during transport.[11]

We do not know whether these differences in timeliness of access to paediatric intensive care and care delivered during stabilisation and transport by PICRTs matter in terms of clinical outcomes and patient experience. It is also unclear what their impact on healthcare costs is. This lack of scientific evidence has led over the years to the evolution of different models of PICRT provision, the development of national standards based on expert opinion rather than scientific evidence, and has contributed to the lack of progress in improving care at the crucial interface between secondary and tertiary paediatric care.

4.2 Study rationale

4.2.1 CLINICAL OUTCOMES FOR TRANSPORTED CRITICALLY ILL CHILDREN

Children cannot choose which hospital to go to when they are critically ill. It is therefore crucial that NHS acute services are organised and delivered in a way that ensures timely, equitable access to high quality care throughout the patient pathway. Each year, nearly 5000 children presenting to general hospitals with life-threatening illness or injury require to be transported by PICRTs to PICUs. Transported children represent one-third of all PICU admissions (and one-half of all emergency admissions). Yet, compared to the two other main patient groups (planned admissions and emergency admissions from within the same hospital where the PICU is located), they have the poorest clinical outcomes: their PICU mortality is nearly double that of planned PICU admissions (8% vs. 4%),[10] and they have a significant risk of long-term complications and considerable associated health and social care costs. It remains unclear whether this is solely because transported children are much sicker than other groups of critically ill children, or whether the timeliness of access to PICU expertise and the quality of care delivered by PICRTs prior to PICU admission may have an additional influence on clinical outcomes.

4.2.2 EXPERIENCES OF TRANSPORTED CRITICALLY ILL CHILDREN AND THEIR FAMILIES

From a family perspective, parents of sick children have described the process of PICU retrieval as the 'the worst journey of their lives'. Studies have shown that families demonstrate evidence of psychological trauma long after acute transfer and admission to PICU.[12, 13] There has been little systematic research into how the patient experience is influenced by timeliness of access to PICU expertise and the quality of care delivered by PICRTs prior to PICU admission, at a particularly vulnerable period in critically ill children's and their families' lives.

4.2.3 RELEVANCE TO NHS SERVICE DELIVERY

Although centralisation of PICUs and the establishment of PICRTs occurred over two decades ago, PICU/PICRT services continue to evolve in response to clinical and financial pressures.[9] The goal of providing high quality care within a 'hub and spoke' model of specialist acute care in a cost effective manner is highly relevant now, and will continue to be relevant well into the future. PICU/PICRT services find themselves facing several clinical pressures such as limited PICU bed availability in the face of increasing demand, especially during 'surge' periods in winter; compliance with expert opinion based national standards which specify that PICRTs should reach the patient bedside within 3 hours;[14] the need for 24/7 transport team availability even during times of high PICU workload; ensuring the availability of adequate numbers of trained staff within the constraints of the European Working Time Directive; and falling numbers of PICU trainees. As other areas of specialist paediatrics are further centralised (e.g. surgery and anaesthesia), concerns have also been raised regarding the deskilling of non-specialist hospital staff, which may lead to delays in the stabilisation of sick children, particularly those with complex health needs. These changes may result in an increase in demand for a more rapid response from PICRTs.[15]

4.2.4 TIMELINESS OF PROPOSED RESEARCH

Acute NHS specialist services such as trauma and stroke care have undergone a process of centralisation over the past decade. Intensive care services for children were similarly centralised in the late 1990s, and dedicated regional PICUs were established. PIC retrieval teams were set up to transport critically ill/injured children from general hospitals to hospitals with PICUs – these specialist teams have been shown to enhance the safety of inter-hospital transport and improve survival in transported critically ill children. However, concerns have persisted regarding how quickly critically ill children at general hospitals can access paediatric intensive care within this centralised model of acute care, and progressive deskilling of staff at general hospitals in the management of critically ill children.

Evidence is urgently required to understand whether and how delays in access to paediatric intensive care and variations in the quality of care provided during acute stabilisation and transport affect clinical outcomes and patient experience. To address this evidence gap, national audit data relating to the referral and transport of critically ill children have been collected by PICANet since 2012. For the first time, these data clearly show national differences in the timeliness of access to paediatric intensive care (time taken by PICRT to reach the patient bedside) and care delivered by

PICRT during transport (team composition, interventions performed and frequency of critical incidents).[20] As the primary conduits through which critically ill children at general hospitals access paediatric intensive care in an emergency, it is plausible that variations in PICRT provision compromise equity of access and may adversely affect their clinical outcomes and patient experience. In the absence of scientific evidence, expert opinion has guided the development of PICRT services and national quality standards over the past decade.

Reconfigurations of specialist paediatric services have been planned to improve the clinical and cost effectiveness of the current models of care, but currently lack a firm evidence base on which to do so. The availability of several years of detailed national audit data through PICANet now makes it possible for the first time to generate the high-quality evidence necessary to guide the development of future standards of care and inform decisions about national policy relating to the care of critically ill children.

5 AIMS AND OBJECTIVES

5.1 Study aims

1. Understand whether and how clinical outcomes and experiences of critically ill children transported to PICU are affected by national variations in: a) timeliness of access to paediatric intensive care, and b) care provided by PICRTs prior to PICU admission.
2. Study the relative cost effectiveness of current PICRT services, and use mathematical modelling to evaluate whether alternative models of PICU/PICRT service delivery can improve clinical and cost effectiveness.
3. Provide evidence for the development of future clinical standards.

5.2 Study objectives

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 a) time from referral to arrival of a PICRT at the patient's bedside, and b) time from referral to PICU admission].

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].

1.3: a) 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.

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

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.

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

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.

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

6 PROPOSED RESEARCH OUTPUTS

Provision of early, high-quality acute care has been shown to improve clinical outcomes in specific diseases such as paediatric sepsis and head trauma.[16, 17] It is unclear how these findings apply to the vast majority of critically ill children who require stabilisation and transport to a PICU by PICRTs. We will examine whether and how timeliness of access to paediatric intensive care and care delivered during acute stabilisation and transport affect clinical outcomes and experiences of critically ill or injured children with a range of diagnoses and pre-existing medical conditions, so that findings can be generalised to all critically ill children.

Positive and negative experiences of families and clinicians will be used to inform the development of new clinical guidelines to ensure that they address the concerns and needs of patients, families and those who care for them. Whilst the stresses associated with PICU are well understood (for both families and clinicians),[13, 18] evidence about experiences associated with PIC retrieval is anecdotal at best. Understanding experiences will enable information, preparation and support to be tailored to the needs of families, with the potential to reduce levels of acute stress and anxiety and improve psychological outcomes in the longer term.

Centralisation of specialist acute care has occurred in several NHS services such as stroke, trauma, and specialist paediatrics.[4, 19] The findings from our research, particularly our novel approaches employing mathematical modelling, can provide evidence that can be generalised to evaluate other such centralisations. This is especially relevant to questions related to the trade-off between timeliness of access to acute care and provision of high quality cost effective specialist care.

7 STUDY DESIGN

DEPICT is a multi-disciplinary mixed-methods study comprising four linked work streams culminating in a series of workshops (See Appendix A for Study Flow Diagram):

A. **Quantitative analysis** of national paediatric intensive care audit data (PICANet) linked to routine administrative data (Hospital Episode Statistics in England and Patient Episode Database for Wales), death registrations (Office of National Statistics) and adult critical care data (Case Mix Programme).
   [This analysis will be conducted retrospectively using data collected as part of national audit during a 3-year period between 2014 and 2016].

B. **Qualitative and questionnaire study** involving interviews of parents of critically ill children transported to PICU (and children themselves, where feasible); interviews with clinicians working in PICUs, PICRTs and acute general hospitals and service managers/commissioners; and questionnaires to collect feedback from parents of transported children.
   [This workstream will involve prospective recruitment of patients over a 12-month period in 2017-18].

C. **Health economic evaluation** of the costs and value for money of different models of PICRTs to identify cost-effective models of service delivery.
   [This workstream will involve analysis of costs and children's outcomes collected as part of the previous workstreams].

D. **Mathematical modelling**, including the use of location-allocation optimisation, to explore the potential clinical and cost impact of alternative models of service and geographical locations where PICRTs could be based.
   [This workstream will involve modelling using the findings of the previous workstreams].

E. **Workshops** involving key stakeholders: children and young people, parents, clinicians, and service managers/commissioners.

The study will involve the participation of all 10 PICRTs and 24 PICUs in England and Wales (representing 21 individual NHS Trusts).

8 RESEARCH PLAN

The study population will be critically ill children and young people (age <16 years) who are transported for emergency admission to a participating PICU in England and Wales.

8.1 Workstream A: Quantitative analysis

The two main objectives of the quantitative analysis are:
Objective 1.1: To study the association between timeliness of access to paediatric intensive care and clinical outcomes, and

Objective 1.2: To study the association between care delivered by PICRTs and clinical outcomes.

8.1.1 STUDY DATASET

We will generate a linked dataset for the study from several data sources:

1. *National paediatric intensive care audit data from the Paediatric Intensive Care Audit Network (PICANet, www.picanet.org.uk).*
   PICANet is commissioned by the Healthcare Quality Improvement Partnership (HQIP) as part of the National Clinical Audit Programme and is based at the Universities of Leeds and Leicester. PICANet data contain detailed clinical information regarding the case mix (age, diagnosis and severity of illness), resource use (daily organ support interventions) and outcome (such as length of PICU stay and vital status at discharge) of critically ill children. Detailed data regarding the transport are also included in PICANet. Data quality is ensured using precise rules and definitions applied by trained local data collectors at each participating unit, and both local and central validation checks to ensure completeness, logic and consistency.

2. *Hospital Episode Statistics (HES, http://content.digital.nhs.uk/hes)*
   Administrative data related to A&E attendances and inpatient admissions to NHS Trusts in England are routinely collected as part of the HES Admitted Patient Care (APC) and Accident & Emergency (A&E) datasets. HES data contain demographic information (age, gender, ethnicity), clinical information (diagnoses and procedures), geographical information (address, site of treatment) and administrative information (time waited in A&E, hospital length of stay). Automatic data cleaning rules are completed at various stages in the cleaning and processing cycle. Similar APC and A&E data for Wales can be accessed from the NHS Wales Informatics Service's Information Services Division as part of the Patient Episode Database for Wales (PEDW).

3. *Death registrations, ONS (http://content.digital.nhs.uk/onsmortality)*
   The Office for National Statistics collects data regarding the date and cause of death, as well as location of death, as part of death registrations in England and Wales. These data can also be accessed through the HES-ONS linked mortality data set.

4. *National adult intensive care audit data, CMP (www.icnarc.org/Our-Audit/Audits/Cmp/About)*
   National audit data are submitted by all adult, general critical care units in England, Wales and Northern Ireland to the Case Mix Programme Database (CMP) at the Intensive Care National Audit and Research Centre (ICNARC). The CMP contains detailed clinical information regarding case mix (age, diagnosis), resource use (organ support interventions) and outcomes (length of stay, vital status at discharge, discharge destination) of critically ill adults and children admitted to adult ICUs.

8.1.2 DATA LINKAGE

8.1.2.1 Purpose of data linkage

While PICANet data contain detailed clinical information regarding the transport, patient case mix, resource use and short-term outcome of transported critically ill children, there is limited information in PICANet regarding the patient pathway immediately prior to transport (such as length of time spent at the referring hospital and wards where the patient was cared for, whether admitted to the adult ICU for stabilisation prior to transport, and interventions performed). Linking PICANet data to HES data (and similar data from NHS Wales) for the acute hospital admission prior to transport and to CMP data (if the patient is admitted to an adult ICU) will provide a clearer understanding of the level of care provided to the child before transport to PICU – these factors are likely to significantly confound the association between timeliness of access to paediatric intensive care and clinical outcome. Therefore, it is crucial that information regarding pre-transport care is available for this study, which we plan to obtain from PICANet data linkage to HES and CMP. Similarly, PICANet data are limited to the PICU stay, which means that longer term outcomes of the patient such as 30- and 90-day mortality as well as healthcare resource use following PICU discharge are not available from PICANet. Data linkage to HES/ONS is vital to ensure that data related to 30-day mortality (study primary outcome), as well as other longer term clinical outcomes (secondary outcomes), is available.

See Appendix B for an example patient pathway for a critically ill child requiring transport to PICU.

8.1.2.2 Study data and generating the linked dataset

We will extract relevant PICANet data related to the transport and the PICU admission episode from all transported admissions to participating PICUs in England and Wales with an admission date during a 3-year study period (1 Jan 2014 to 31 Dec 2016). To ensure a high-quality dataset, we will apply a series of data cleaning rules including individual data range checks and inter-variable validation to the study data set to identify and clean common and obvious data quality errors prior to analysis.

We will apply for HRA CAG approval for this study. See Appendix C for data flows during the linkage process.

Data linkage will be undertaken by the NHS Digital Data Access Request Service (DARS) acting as a 'trusted third party'. PICANet have experience of successfully linking PICANet data to HES/ONS data through HSCIC in the past. The availability of NHS numbers in a very high proportion of PICANet (98%) and CMP records for children (97%) provides reassurance that most records can be successfully matched using a minimal number of patient identifiers. PICANet data, including identifiers, is currently held at the University of Leeds. University of Leeds will upload a list of patient identifiers (NHS numbers, date of birth, name and postcode) and a unique DEPICT study number to secure servers at NHS Digital for a cohort of children admitted to PICUs in England

during a 3-year period (2014-16) – Dataset 1. Similarly, ICNARC will upload a similar list of patient identifiers and a unique local CMP identifier for children admitted to AICUs in England during the same 3-year period (2014-16) – Dataset 2. No clinical information will be transferred to NHS Digital. NHS Digital will first merge Dataset1 with Dataset 2. The merged dataset will then be linked to HES/ONS data. A pseudonymised dataset consisting of DEPICT study number, Unique CMP identifier, and HES/ONS data will be returned from NHS Digital to the University of Leicester. University of Leicester will send a list of DEPICT study numbers to University of Leeds and a list of unique CMP identifiers and corresponding DEPICT study numbers to ICNARC. University of Leeds will send PICANet clinical data for the DEPICT study numbers to the University of Leicester. Similarly, ICNARC will send CMP clinical data for the DEPICT study numbers to the University of Leicester. The final pseudonymised study dataset containing only the study number will be held at the University of Leicester for analysis. NHS Digital will follow established procedures to destroy patient identifiable data once the linkage has been completed.

Data linkage for A&E and Admitted Patient Care (APC) data for care received in Wales will be conducted by NHS Wales Informatics Service in a similar flow as for the English data. A list of eligible NHS numbers and a unique DEPICT or CMP study identifier will be passed from PICANet and ICNARC to NHS Wales. NHS Wales will identify which NHS numbers appear on both lists and this will be used to link each child with their hospital A&E data and data related to their clinical care. Matching will consider the fact that some children may be admitted to hospitals or PICUs on more than one occasion throughout the study period. This data will be passed to the University of Leicester in a pseudonymised form (i.e. the NHS number removed but the DEPICT and CMP study identifiers will remain). The University of Leeds and ICNARC will then pass clinical data to the University of Leicester using the DEPICT or CMP study identifiers to allow the data sources to be combined with the A&E and APC data from NHS Wales.

Matching will consider the fact that some children may be admitted to hospital (and PICU) on multiple occasions within the study period.

8.1.3 DATA ANALYSIS

The study statistician will employ established approaches to develop statistical models to study the association between timeliness of access to paediatric intensive care and clinical outcomes (Objective 1.1), and the association between care delivered by PICRTs and clinical outcomes (Objective 1.2).

8.1.3.1 Clinical outcomes

Primary outcome: Mortality within 30 days following PICU admission (the first admission in case of multiple PICU admissions), established by data linkage with death registrations.

Secondary outcomes to include:

a) Mortality at fixed time-points (PICU discharge, 90 days and 1 year following [first] PICU admission)
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
g) Hospital resource use (total number of days admitted to hospital) in the 12 months following discharge from the first PICU admission.

8.1.3.2 Model 1: Timeliness of access to paediatric intensive care

Timeliness of access to paediatric intensive care will be measured by:
a) Time from acceptance of the referral by a PICRT to arrival of the PICRT at the patient bedside, and
b) Time from acceptance of the referral by a PICRT to arrival of the patient on the PICU.

8.1.3.3 Model 2: Care delivered by the PICRT

Three aspects of care delivered by the PICRT will be studied:
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.

8.1.3.4 Model development

Prior to model development and data analysis, we will discuss and finalise a statistical analysis plan, which will outline the statistical methodologies to be employed during the analysis and a strategy for addressing confounding and how we will deal with missing values. A draft statistical analysis plan will be discussed at the first study steering committee (SSC) meeting during months 4-6 and finalised over subsequent months.

The overall strategy for the model development will consist of three main steps: 1) to identify potential confounding variables (both measured and unmeasured) and to select appropriate confounders available from the linked dataset for inclusion in the analyses; 2) to utilise carefully considered traditional regression models as well as propensity scores to draw inferences regarding the effect of key factors on patient outcome; and 3) to investigate the issue of unmeasured

confounding using instrumental variable analysis and perform sensitivity analyses to estimate the effects of unmeasured confounders on our findings.

1) Identifying potential confounding variables and selection of variables for model development

In the first instance, we will draw upon the expertise of clinical applicants and PICANet to generate a list of potential confounding factors. We expect the main confounding variables to be severity of illness (main diagnosis leading to PICU admission, ventilation status at referral and the Paediatric Index of Mortality 2 score) and the receipt of intensive care interventions prior to the PICRT arriving at the patient bedside. Intensive care interventions carried out by the general hospital team prior to the arrival of the PICRT are recorded in PICANet; we will also include as confounders the time spent at general hospital prior to being referred/accepted for transport to PICU (from linked HES data), and care provided in an adult intensive care unit (from linked CMP data). We will seek additional input from clinical applicants at monthly PMG meetings during months 4-12 of the project to further refine this list. We have also scheduled a Study Steering Committee (SSC) meeting during months 4-6, at which clinical members (medical/nursing/allied health professionals) will help further refine the list of confounders. In this way, we will obtain extensive expert clinical input into the choice of potential confounding variables that could be included in the model development; we will also generate clinical knowledge regarding the mechanisms by which variables may influence the exposure status and outcome.

Based on the clinical knowledge generated through the above process, we will produce directed acyclical graphs (DAG) to visually examine the assumptions regarding the causal structure of the variables being analysed and to help decide which variables should be included as confounders. The visualization of the process will also help in the identification of measurable factors that might serve to block a backdoor path including an unmeasured (or unmeasurable) confounder. It will also serve to allow the effect of any likely bias induced by unmeasured confounding to be estimated. DAGs will also help differentiate confounding variables (variables that affect the outcome and have an association with the exposure status) from variables that could potentially be used as instruments in the instrumental variable analysis (variables that affect the exposure status but not the outcome, other than through the exposure). The final DAG will be derived by consensus where possible, or by a majority view of the experts involved if necessary.

2) Draw inferences regarding the effect of key factors on patient outcome

Before any modelling work is undertaken, we will do a thorough descriptive analysis of the datasets and look for potential issues that would need to be addressed at an early stage, such as a large proportion of missing data for key confounders or an unusual distribution of age/weight/diagnosis or other risk factors. Prior to multivariate modelling, we will explore univariate associations between key explanatory variables (timeliness, care delivered) and potential confounders with our stated primary and secondary outcomes. All explanatory variables and confounders with significant univariate association with outcome will be considered in the regression modelling for Models 1 and 2.

We will develop statistical models to study the association between timeliness of access to intensive care and clinical outcomes, and the association between care delivered by PIC retrieval teams and clinical outcomes. Since we recognise that the data could potentially be clustered by PICRT, we will develop multilevel models as appropriate (to include the random effects of PICU/PICRT/general hospital) depending on the outcome:

- Mortality at fixed time-points: logistic regression
- Length of stay (PICU, hospital), resource use in PICU and hospital resource use following PICU discharge: linear, Poisson or negative binomial regression models (as appropriate) and survival models
- A&E attendances: Poisson or negative binomial regression model (as appropriate)

For both Model 1 and Model 2, several multivariate models will be developed and Akaike Information Criterion (AIC) used for further model selection. We will also use cross-validation methods alongside an examination of model residuals and leverage, to ensure we are not over-fitting. Different models will contain different combinations of the potential confounders, which will be chosen from a set. We will also include other risk factors within the models, including patient- and organisation-level factors (but not limited to): patient age, weight, ethnicity, index of multiple deprivation, co-morbidities, geographical region, distance from PICRT base to referring hospital, distance from referring hospital to admitting PICU, season (summer: Mar-Aug vs. winter: Sep-Feb) and bed occupancy of the nearest PICU. For each model, we will carefully consider the inclusion/exclusion of confounders that could mask the effect of timeliness (e.g. distances; PIM-2 score) or team composition (geographical region, if this is a key determinant of team composition).

We will also analyse the data using propensity scores – this technique will help us to include a large number of confounders in the analysis.

3) <u>Investigating unmeasured confounding</u>

We will primarily use instrumental variable analysis to study the effect of unmeasured confounding in this study. Identifying a suitable instrumental variable (IV) in this setting is likely to be challenging, since it needs to satisfy three key assumptions: a) the IV must not be correlated with patient outcome, except through the effect of the exposure; b) the IV must be highly predictive of the exposure; and c) the relationship between the IV and the exposure must not be confounded. Because the first assumption is empirically unverifiable, the choice of the instrument heavily relies on expert clinical knowledge – we will propose and discuss various candidate instruments at the PMGs and the first SSC meeting (months 4-6). The choice of the 'best' instrumental variable will be finalised as part of the analysis plan, based on clinical and statistical input. We anticipate that candidate IVs will include variables such as distance to the referring hospital (nearby hospital versus distant hospital) and activity level at the time of referral (based on number of other ongoing retrievals within the retrieval service at the time of referral). We will also use sensitivity analyses to estimate the effect of unmeasured confounding on our study findings.

8.1.3.5 Sample size calculations

PICANet data from 2014/15 indicates that the 30-day mortality rate for transported PICU admissions is approximately 7% and that PICRTs reach critically ill children within 3 hours of referral acceptance in 85% of cases. Accounting for the potential for clustering of data by PICRTs, we calculate that a minimum of 9685 transports would allow us to detect a 3% difference in 30-day mortality between the two groups (transports taking ≥3 hours to reach patient bedside and transports taking <3 hours to reach patient bedside) with 80% power and alpha 5%. We will analyse PICANet data from transported PICU admissions over a 3-year period (nearly 15,000 transports) to ensure adequate sample size for our analysis.

8.2 Workstream B: Qualitative and questionnaire study

This work stream will address the following two objectives of the DEPICT study:
Objective 1.3: To explore parents', and where feasible children's, experiences of emergency transport to PICU, and
Objective 1.4: To explore clinicians' and service managers'/commissioners' perspectives of PICU transport and its impact on care provided to critically ill children and young people, and the wider impact on other patients and services.

We will employ a mixed-methods approach with a convergent triangulation study design whereby quantitative and qualitative data will be collected concurrently, with equal weight being given to both work streams. We will integrate findings from the qualitative and questionnaire study (how do national variations in the timeliness of access to emergency intensive care and care delivered by PICRTs affect patient/family experience?) with findings from the quantitative study (how clinical outcomes are affected by national variations) at the interpretation stage to generate complementary views of paediatric retrieval. Uniquely, the qualitative study will gather rich narrative detail from patient experiences and clinician perspectives that cannot be obtained from quantitative analyses of routine data.

See Appendix D for schedule of procedures involved in the qualitative and questionnaire study. See Appendix E for the data flow involved in the qualitative and questionnaire study.

8.2.1 RECRUITMENT OF TRANSPORTED CHILDREN AND THEIR PARENTS

Parents of all critically ill children and young people transported to one of the 24 participating PICUs in England and Wales during a 12-month period (and where feasible, the children/young people themselves) will be eligible for recruitment to the qualitative and questionnaire study. Transport may have been performed by PICRTs or, less commonly, by other transport teams.

Clinical staff at each participating PICU will screen for eligible participants at PICU admission. Participants (parents and children/young people) who meet the inclusion criterion will be approached by suitably qualified and trained clinical/research staff to discuss the study. Written informed consent will be sought from eligible participants:

a) for completion of a questionnaire relating to the experience of PIC transport;
b) to be contacted by a qualitative researcher based at Great Ormond Street Hospital for potential participation in an interview at a later date;
c) to be contacted by the qualitative researcher for completion of quality of life questionnaires 12 months later; and
d) for the use of patient identifiers to extract data from PICANet relating to the individual child's transport episode.

A detailed study information sheet will be provided. Adequate time will be provided for parents and children/young people to consider taking part in the study. It is anticipated that the majority of children/young people will be too young and/or too ill to participate directly in the consent process; however, age-appropriate information sheets and assent forms will be used where appropriate.

8.2.1.1 Bereaved parents

It is possible that some children may unfortunately die before the clinical/research staff have the opportunity to discuss participation in the study with their parents. In this situation, we do not intend to exclude parents from participating in the research; excluding parents of children who die will also introduce selection bias into the study. Recognising that the standard consent processes will not be suitable for these situations, after consultation with parent co-applicants and the Study Steering Committee, we have developed a separate consent process for this subgroup of parents. We have also developed versions of the participant information sheet and consent forms for bereaved parents. Parents will be approached several weeks after the child's death (timing left to the discretion of the clinical team involved in the care of the child) by means of a personalised letter sent from the study Principal Investigator (PI) for the relevant research site. Enclosed with the personalised letter will be the appropriate participant information sheet, two self-complete consent forms and two copies of the transport questionnaires. Bereaved parents will be invited to participate in the study (to complete the transport questionnaire and agree to be contacted for participation in an interview, but not for the 12-month quality of life questionnaire). If the parents decide to participate in the study, they will be able to return the signed consent form(s) in a reply-paid envelope. Completed transport questionnaires will be returned in a separate reply-paid envelope or completed online (see below).

8.2.2 <u>QUESTIONNAIRE STUDY</u>

Clinical/research staff at each participating PICU will give a paper questionnaire to parents who consent to completing a questionnaire relating to the experience of PIC transport. Based on our ongoing research experience of collecting long term follow up information from children transported by the CATS team (BASIC, NIHR portfolio ID 15920) we will also offer parents the option to complete this questionnaire electronically using a secure online system (only centre and study numbers will be used; no identifiable data will need to be entered into the questionnaire). Wherever possible and relevant, both parents will be offered the opportunity to complete the

transport questionnaire individually if they were present for some of their child's transport to intensive care, recognising that parents may have different perspectives and capturing both viewpoints would enrich the description of family experiences.

We recognise that some patients will be from families who do not speak/write English and that these families may generally have a poorer experience of health care. Therefore, we will discuss with different PICRTs, and arrange for the information leaflet, consent form and transport questionnaire to be translated into the 5 most commonly spoken languages (other than English).

We will develop the questionnaire from similar existing questionnaires and from relevant literature, and use the experience of the study team, the steering group and parent representatives to further inform its format and content before it is finalised.

The questionnaire will seek parental responses to specific questions regarding their experience during and after their child's transport to PICU. We will cover aspects such as how long they waited for a PICRT to arrive, what information was provided regarding the transport process, expectations of the transport and whether these were met, medical staff involved from the PICRT, whether parents were able to accompany their child in the ambulance, duration and experiences of the journey and handover on arrival at the PICU, and whether they felt informed and involved in their child's care. We will use a mixture of rating scales, tick box questions and free text boxes; the questionnaire will be designed to take no longer than 15 minutes to complete. We will pilot the questionnaire first to ensure that it is acceptable to parents. Parents will be given a reply-paid envelope to return the questionnaire directly to the study team or, if they prefer, they will be able to return the questionnaire to a study collection box on the PICU.

Since postal response rates to questionnaires are typically about 20-25%, we anticipate receiving 800-1000 completed questionnaires (around 4500-5000 critically ill children are transported to PICU by PICRTs each year). We will link data from the questionnaires with PICANet audit data collected for that particular transport to provide additional information for the analysis (e.g. time to arrive at bedside).

8.2.3 PARENT INTERVIEWS

8.2.3.1 Sampling

We aim to recruit approximately 5 parents of children/young people transported by each of the 10 PICRTs across England and Wales for participation in an interview (total of approximately 50 interviews). This number will be sufficiently large to enable us to capture the range of parents' experiences across the different models of care and to reach data saturation, whilst being mindful of the resource implications and feasibility of collecting and analysing large amounts of interview data within the project time-frame. We will select eligible participants from the cohort of parents who have consented for the interview, using sampling criteria as below:

- Patient age: infant (<1 year), young child (1-4 years), older child (5-12 years), teenager (13-16 years)
- Main diagnosis: severe infection, cardiac disease, trauma, neurological disease, other
- Pre-existing health condition: none, at least one pre-existing health condition
- Timeliness of access to intensive care: ≥3 hours, <3 hours from referral to PICRT arrival at patient bedside
- Patient's home location: rural, urban
- Whether the parent accompanied the child in the transport to the PICU (yes; no)

Across the PICRTs, this purposive sampling strategy will ensure diversity in terms of the child/young person's underlying condition, new/existing disease/injury, rural/urban location, distance to PICU and time taken for the PICRT to reach the patient bedside. Further, since we will have sampled from each of the PICRTs, there will be diversity in terms of the variations in care delivered by the PICRTs (team composition, interventions performed during transport). Finally, we will aim to ensure diversity in terms of ethnicity and socioeconomic status.

8.2.3.2 Recruitment

The details of parents who have consented for potential participation in interviews will be passed on to the qualitative researcher who will be conducting the interviews. The researcher will contact eligible parents approximately 2 to 3 months after PICU transport to confirm that they still wish to participate, answer any questions they might have about the study, and arrange a mutually convenient time and location for the interview to take place. Further written consent will be obtained at the time of interview to confirm that parents agree to participate and for their interview to be recorded. Interviews will be conducted face to face wherever possible, but if parents prefer, telephone or Skype interviews will also be facilitated. If necessary, interpreters will be arranged to ensure that non-English speaking families are able to participate if they wish.

8.2.3.3 Interviews

As described above, we aim to recruit parents of approximately 50 children/young people transported to PICU. This number will enable us to interview parents who represent each of the retrieval models from different PICRTs, thus allowing us to capture important elements of the experience of different models, whilst at the same time ensuring that the number of interviews is feasible to conduct and analyse in the time available. The interview guide will focus on parents' experiences prior to, during, and after transport to PICU with the aim of obtaining a more in-depth understanding than will be possible from the questionnaires. Particular areas of focus will aim to understand what specific aspects of the retrieval parents (and/or children) experienced as working well; what they think would constitute an 'ideal' or optimum transport to PICU; what aspects participants felt worked less well and what could have been done to improve their experience. The interviews will provide greater insight into what a 'high quality' retrieval looks like from the perspective of parents. Interviews are expected to last between 1-2 hours, with appropriate breaks

if necessary, recognising that parents will be revisiting a difficult and upsetting time in their lives. Interviews will be audio-recorded and transcribed verbatim.

8.2.4 CHILDREN'S AND YOUNG PEOPLE'S PERSPECTIVES

Where feasible, children and young people will also be recruited to provide feedback about their experiences during transfer to PICU. Whilst it is acknowledged that the majority of children/young people will be too young and/or too ill at the time to recollect their transfer to PICU, there may be some who will be able and willing to share their experiences.

8.2.4.1 Sampling

We will endeavour to use a diverse sampling strategy to recruit 20-30 children/young people from across the different PICRTs (although if it feasible to recruit up to 5 from each of the 10 PICRTs we will do so), focusing on recruiting children who were transported to PICU for different underlying reasons and via different PICRT models. Whilst we hope that there will be diversity within the sample in terms of elements such as urban/rural location, main diagnosis, and existing/new condition, we are also aware of the challenges of recruiting eligible children, so our recruitment strategy will be more flexible. We envisage that most, but not necessarily all, will be children of parents recruited for interviews.

8.2.4.2 Recruitment

Children and young people will be eligible for recruitment if they fulfil the following criteria:

- Aged between 5 and 16 years
- Able to remember at least some of their transfer to PICU
- Able to provide age-appropriate assent for their participation
- Parent(s) has provided consent for their child's participation

Recruitment of children will be along similar lines as described above, except that written assent will be obtained from children for their own participation, using an age-appropriate assent form.

8.2.4.3 Interviews

We will use a range of creative methods to engage children/young people, including activities such as 'draw and write',[21] 'Talking mats',[22] and third-person craft activities, and a conversation will be developed around the use of these materials. Sessions will be audio-recorded, photographs taken of any creative outputs and notes made immediately after the session about aspects such as the children's engagement, ability to recall and impact of revisiting the time of their transport to PICU. We will explore with the children their experiences of being transported to PICU, dependent on what they can recall, focusing on the time before, during and immediately after the transfer. Recognising that this is likely to have been a distressing time for children, the researcher will be particularly sensitive to, and careful about, how these experiences are explored. If children would like their parents to be present, this will be facilitated. Sessions are expected to last 30-60 minutes, to enable time for rapport building with children at the start of the session and some appropriate

"ending" of the session before they leave. Members of the research team have experience of using creative methods and interviewing children, and any training in the use of specific methodologies will be provided to the researcher.

8.2.5 CLINICIAN AND SERVICE MANAGER PERSPECTIVES

8.2.5.1 Sampling

We will use a purposive sampling strategy to identify and recruit 35-40 healthcare professionals from PICRTs, PICUs and acute general hospitals. Use of a sampling matrix will ensure diversity in terms of professional background, experience, place of work (local hospital, dedicated transport team, PICU-run transport team, PICU), rural/urban location and number of emergency transfers. We will also recruit 4-8 service managers/NHS commissioners for interviews.

8.2.5.2 Recruitment

Local PIs at PICRTs will be asked to identify at least 5-6 eligible professionals from within their own service, the PICUs they serve, and acute general hospitals in their region, as well as local service managers/commissioners. Study information and an invitation letter to participate in the interview will be provided to eligible participants. If they are willing to participate, participants will be asked to consent to their details being passed to the researcher who will be conducting the interviews. On receiving the details, the researcher will contact them to check that they still wish to participate, answer any questions they have about the study and arrange a mutually convenient time for the interview to take place. Professionals will be offered the opportunity to participate in a telephone or face-to-face interview, depending on their preference. Prior to the interview commencing the researcher will ask the professional to provide further consent confirming agreement to participate and for recording the interview.

8.2.5.3 Interviews

Semi-structured interviews will be conducted to elicit staff experiences and perceptions of the transport of critically ill or injured children/young people, the impact of the service on the care provided to the children/young people themselves, and any wider impact on other patients and services. A topic guide will be developed based on relevant literature and the experience of the study team/steering group, and will be piloted with 3-4 clinicians prior to beginning the interviews. Interviews are expected to last 30-45 minutes and will be recorded and transcribed verbatim.

8.2.6 DATA ANALYSIS

Interview data will be entered into Framework, a matrix based approach, which facilitates rigorous and transparent data management. The method involves five distinct, but highly interconnected stages: familiarisation; identifying a thematic framework; indexing; charting; mapping and interpretation. The approach enables data to be examined within cases across a range of different themes, thereby facilitating comparisons to be made both between different models of retrieval and within PICRTs. Use of Framework is also well suited to research involving group- and individual-level analysis. The data will be managed using NVivo, a qualitative data analysis programme.

Questionnaire data will be analysed using descriptive statistics to describe and compare the different PICRT models and to examine associations between key variables (frequencies, medians and inter-quartile ranges, Spearman's correlations, Mann-Whitney, Chi-squared and Kruskall-Wallis analysis of variance, as appropriate).

8.2.7 WITHDRAWAL FROM STUDY

Participants will have the right to withdraw from the study at any time after consent. Data collected up to the point of withdrawal will be used unless the participants expressly did not wish researchers to use the data.

During recruitment of participants for interviews, the researcher will contact consented parents approximately 2 to 3 months after PICU transport to confirm that they still wish to participate and to answer any questions they might have about the study. Similarly, at 12 month follow up, parents will be contacted to confirm they still wish to participate in the study and to complete follow up questionnaires. If the parents wish to withdraw from the study, they can do so at any time without providing a reason; if a reason for withdrawal is provided, it will be recorded.

8.3 Workstream C: Health economic evaluation

This work stream will address the following objective of the DEPICT study:
Objective 2.1: To perform cost effectiveness analyses of PICRT provision for critically ill children, comparing different service models currently in use.

8.3.1 APPROACH

We will evaluate the costs and value for money of different ways PICRTs are currently organised to identify the most cost-effective model. The data sources described in the quantitative analysis (workstream A) will be supplemented with cost data and the assembled dataset of individual observational patient-level data will be used to compare different PICRT models. The primary health outcome measure for the health economic evaluation will be the number of lives saved in each strategy, and the secondary outcome will be quality-adjusted life years. A detailed cost analysis of each identified PICRT model will be undertaken based on team composition, interventions performed and critical incidents. The statistical analysis will aim to identify differences in lives saved, QALYs gained and cost differences between different ways in which PICRTs are organised. We will evaluate costs and mortality at 30 days following PICU admission (the primary outcome in the quantitative analysis; short-run analysis), costs, mortality and QALYs at one year following PICU admission (the final follow-up point in the study; medium-run analysis), and lifetime costs and QALYs (long-run analysis). A UK NHS and personal social services (PSS) perspective will be adopted for the short- and medium-run analyses, though PSS cost are expected to be small; in the long-run analysis, an NHS/PSS perspective will be adopted in the base case and a societal perspective will be adopted in sensitivity analysis.

8.3.2 MEASURING COSTS

There are three elements of the cost analysis: costs of PICRT transport; NHS/PSS costs in the short- and medium-run; and, NHS/PSS and societal costs in the long-run. A detailed cost analysis of transport by the PICRT will be carried out based on travel time, team composition, interventions performed and management of critical incidents. Unit costs for each of these items will be obtained from provider Trusts and 2014-2015 NHS Reference costs.

For NHS/PSS costs in the short- and medium-run, the main health care resource use categories following arrival at the PICU will include time spent in the PICU (also accounting for time on invasive ventilation, vasoactive agent therapy, renal replacement therapy and extra-corporeal life support), time spent on different wards in the hospital after discharge from the PICU, and the number of inpatient and day case admissions, A&E visits and outpatient visits up to one year. Unit costs for these items will be taken from 2014-2015 NHS Reference Costs. It will not be possible to measure costs outside the hospital during the first year (e.g., primary care costs) directly for each patient included in the analysis, but we will estimate these based on published estimates of primary care resource use associated with main diagnosis leading to PICU admission. These will be obtained from systematic literature searches. While there is considerable uncertainty in these costs, we expect them to be a small proportion of total costs when combined with hospital costs. Hence the uncertainty is unlikely to affect the results, though we will examine this in sensitivity analyses.

Long-run costs will be modelled from published sources based on systematic literature searches of the CEA Registry at Tufts University, the NHS Economic Evaluations Database, the Health Technology Assessment Database, the Research Papers in Economics Database and PubMed. These will include NHS/PSS and societal costs where possible. We will aim to identify published estimates of incremental discounted lifetime costs from NHS/PSS and societal perspectives associated with main diagnosis leading to PICU admission. Where these are not available directly we will compute annual incremental costs by age and model lifetime costs applying survival estimates and recommended discount rates.[23] Given the uncertainty in these estimates we will undertake extensive sensitivity analyses (see below).

All costs will be reported in 2015/2016 prices, inflated where necessary using published inflation indices.[24]

8.3.3 MEASURING OUTCOMES

For the short- and medium-run analysis, mortality up to one year will be measured directly in the study, as described in work stream A. Quality of life will be assessed at 12 months and used to compute QALYs for the medium-run analysis. As described previously, families will be consented during PICU admission for completion of quality of life questionnaires at 12 months follow-up. We expect most children to be under 5 years of age at PICU admission (approximately 50% of the transported children will be under 1 year of age, 25% will be aged 1-5 years, and 25% over 5 years). Measuring health-related quality of life suitable for estimating QALYs in this age group is

challenging, and we therefore propose to use two methods: HUI-2 measured via proxy assessment by the parent and the PedsQL mapped to EQ-5D scores.[25, 26] As children recruited to the study are initially critically ill, completion of quality of life measures at baseline will not be possible, and so as is normal in critical care studies an assumption about baseline quality of life for the cohort will be made, e.g. assume a value of zero at baseline.[27, 28] For survivors at 12 months, QALYs will be calculated using the utility scores at 12 months assuming utility score of zero at baseline, and a linear interpolation between baseline and 12 months. For decedents between baseline and 12 months, we will assume zero QALYs. For the long-run analysis, utility data will be obtained from published sources including: the CEA Registry at Tufts University, which contains a searchable database for utility weights by e.g. diagnosis; the NHS Economic Evaluations Database; and systematic searches of the wider literature for quality of life information suitable for estimating QALYs e.g. using PubMed.

8.3.4 ANALYSIS

Using these methods we will produce a patient-level dataset of costs and outcomes in the short-, medium- and long-run for every patient. Analyses of the mortality data will be as described above. QALYs will be analysed using a similar approach using linear models. Cost data are likely to be skewed and so to analyse these data (at 30 days, one year and lifetime) we will use a generalised linear model with gamma family and log link,[29] but will consider using other functional forms, such as Normal, Gaussian, inverse Gaussian and negative binomial distributions, selecting the model that gives the best fit of the data in terms of residual plots and the Akaike Information Criterion. We will also follow current guidance on conduct of economic evaluations using observational data to assess the main assumptions for addressing selection bias in the statistical models implemented.[30] The regression analyses will estimate lives saved, differences in costs, and QALYs gained between different PICRT models. Cost-effectiveness will be measured using incremental net monetary benefits (NMBs) calculated at different values of the willingness to pay to avoid one death or gain one QALY.

There will be considerable uncertainty in our estimates, especially in the long-run analysis. We will investigate this extensively using deterministic and probabilistic sensitivity analysis. Parametric and non-parametric bootstrap methods will be employed to evaluate uncertainty around differences in the lives saved, QALYs gained, costs and NMB, and we will construct cost-effectiveness acceptability curves.

The main outcome of the health economic analyses will be estimates of the costs and benefits of different PICRT models in the short-, medium- and long-run using a variety of cost and outcome measures, including point estimates and uncertainty intervals. We will follow current guidance for methods of technology appraisal to present and report the results of the economic analysis.[31] We will also estimate the budget impact if each PICRT model were to be rolled out nationally based on projections of need for PICRT services.

8.4 Workstream D: Mathematical modelling

This work stream will address objective 2.2 of the DEPICT study:
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 without increasing overall cost.

This work will build directly on the quantitative analysis (work stream A) and the health economic evaluation (work stream C), but will also incorporate insights gained from the qualitative work (work stream B).

8.4.1 APPROACH

The quantitative analysis (work stream A) will reveal which factors are the most important drivers of outcome for the child after emergency transport to PICU: for instance, this might be as specific as the distance the PICRT has to travel or the interventions provided by the PICRT once at the bedside. Or, the factors could be broader such as overall time to bedside or overall time from referral to PICU arrival. We will use mathematical modelling and optimisation methods to explore the potential impact on outcome of different possible models of service that could impact the identified drivers of better outcomes. For instance, possible alternative models could include:

- more transport services (to reduce distance) (either with same number of teams or more teams)
- the same number of transport services with more teams (to reduce time to bedside by having more teams available to go out)
- seasonal allocations of teams (to plan for the winter surge)
- changes to team composition, perhaps varying by region/season.

In such modelling, we will also use location-allocation optimization to investigate, for a given number of transport services and teams and a set of possible locations, where PICRTs should be based to minimise travel time to the local hospitals they serve and to the receiving PICUs. The constraints on the numbers of services, numbers of teams and possible locations will be defined through conversations with the PICRT services and commissioners.

Potential service models will also take into account the views of parents and staff, in particular where there are options that are clearly preferred and would not negatively affect the child's eventual outcome. Any proposed service models will be further re-examined in light of the feedback from stakeholders (parents and families, PICUs, PICRTs and local hospital clinicians) from the workshops (work stream E). We will also combine the results of this modelling strand with the cost-effectiveness analysis to explore how different potential models might affect the cost-effectiveness of the service.

8.4.2 ESTABLISHING THE CORE DATASET AND DISTANCE/TIME LOOKUP TABLES

We will compile a dataset suitable for use in location/allocation analysis. This will involve collating data on the location of all hospitals in England and Wales that could act as a point of demand for transfer to a PICU and the location of PICUs themselves. We will explore gaining access to the SHAPE tool curated by Public Health England that contains these data (https://shape.phe.org.uk), including some detail on journey times between sites. Additionally, through discussion with commissioners and PICRT services, we will identify the set of potential locations for retrieval service teams, which will be a subset of the set of PICUs. We will also explore the approach used by Harper et al. for the Welsh ambulance service.[32] We will use their free tool, PatMap (https://github.com/JasYoung314/PatMap), to do this, which is based on Google Maps. This will result in a set of extensive look up tables containing the journey distances and expected journey times between potential locations of retrieval services, points of demand at local hospitals and PICUs.

8.4.3 SETTING UP A LOCATION MATHEMATICAL MODEL

Using the location/time dataset prepared earlier we will first develop a "coverage" discrete location model drawing on standard approaches from the operational research (OR) literature.[33] Essentially this coverage model will be used to identify the smallest set of PICRT locations and the attendant allocation of hospitals to PICRT "catchment areas" that ensures that each hospital is served by a PICRT positioned such that the distance travelled by retrieval teams or the time taken to retrieve sick children is below some threshold value. The use of travel distance or travel time and the choice of an acceptable threshold value will be informed by the statistical analysis in work stream A, the interviews in work stream B, and further discussion with key stakeholders. In this standard approach, we are looking for the fewest number of PICRT services that allow for full coverage of the country within defined time and distance constraints and then where they should be located.

8.4.4 SETTING UP THE OBJECTIVE FUNCTION FOR THE LOCATION-ALLOCATION OPTIMISATION MODEL

Using the same dataset, we will develop an alternative form of location optimisation model that can be used identify PICRT locations that, as a set, minimise the mean expected time taken for the retrieval team to arrive at the referring hospital (or the mean expected time taken to get children to PICU if the analysis in work stream A suggests this is more appropriate) based on there being a certain number of retrieval services nationally.[34] In this approach, we are locating PICRTs to try to minimise the time to bedside across the country given a maximum number of PICRT services.

8.4.5 EXPLORING THE OPTIMAL NUMBER OF TEAMS AVAILABLE FOR EACH PICRT

The two different optimisation models developed previously do not incorporate decisions as to the number of teams available for each retrieval service. Queueing theory such as that deployed by Pagel in previous work for the CATS retrieval team will be used to determine the relationship

between referral rates, the number of retrieval teams that a service has, and the expected time to a team being available to despatch. We will also investigate whether the application of hypercube queuing models as first developed by Larson to optimise the location and number of emergency service vehicles could be adapted for the PICRT context.[35] Developed models for this stream are likely to need heuristic solution algorithms and the locations and allocations suggested by the previous analyses will then be used as starting solutions in a heuristic search to give locations and team numbers that minimise the total number of teams required to meet a particular service standard or to give the best service that uses a fixed number of teams.

8.4.6 ADDING HEALTH OUTCOMES TO THE OPTIMISATION MODELS

Finally, we will explore the scope for extending the analysis to identify PICRT team sizes and locations that, as a set, maximise expected survival based on patterns of forecasted demand and a causal interpretation of the statistical associations identified between factors influenced by location of PICRTs and clinical outcome from work stream A.

8.5 Workstream E: Synthesis of findings and workshops

We have employed a multi-method approach to draw together findings from the various work streams (see Flow Diagram for relationship between the work streams, and the framework for how and when they will be integrated with each other). Feedback from stakeholder workshops will help refine the study findings to generate new evidence in the field of paediatric retrieval.

We will arrange two workshops for families (children and young people, and parents) in different geographical locations to present the preliminary results of the work streams and to collect their feedback. Feedback will be instrumental in informing any final analyses required within the health economic evaluation and the mathematical modelling strands. Similarly, two similar workshops will be arranged for clinicians, with their input used to refine any final analyses. A key stakeholder workshop (families, clinicians, commissioners) will be held at the end of the study to present and synthesise results from each strand of work to provide evidence to inform the development of future national standards and information resources for parents. Workshop participants will be asked to consent to the sessions being audio-recorded, with assurance that no individual contribution will be directly attributable to them in any outputs.

8.6 End of the study

The end of the study will be the date of completion of the 12 month follow up questionnaires for the last patient recruited to the qualitative study.

9 ETHICAL CONSIDERATIONS

The quantitative analysis of routine audit data linked to other data sources raises ethical issues related to:

1. Collection and use of patient-identifiable data: We will not separately collect patient identifiable data for the purposes of this study without patient consent. The study dataset for the quantitative analysis will only utilise pseudonymised data (see linkage section below). The two main national audits involved in this research, the Paediatric Intensive Care Network (PICANet) and the Case Mix Programme (CMP), both currently collect and process identifiable information as part of their national audit role. Collection of personally identifiable data without explicit consent for PICANet has been approved by the Patient Information Advisory Group, now the NHS Health Research Authority Confidentiality Advisory Group (HRA CAG), and ethical approval granted by the Trent Medical Research Ethics Committee, ref. 05/MRE04/17 +5. Similarly, Section 251 support for the collection and use of patient identifiable data has been approved for the Case Mix Programme by the HRA CAG - Approval Number: PIAG 2-10(f)/2005.
2. Data linkage: Since linkage of data for this study is not currently covered by the existing Section 251 approvals, we will apply for HRA CAG approval for this study. Data linkage will be undertaken by the NHS Digital Data Access Request Service (DARS) acting as a 'trusted third party'. PICANet have experience of successfully linking PICANet data to HES/ONS data through HSCIC in the past. The availability of NHS numbers in a very high proportion of PICANet (98%) and CMP records for children (97%) provides reassurance that most records can be successfully matched using a minimal number of patient identifiers. PICANet data, including identifiers, is currently held at the University of Leeds. University of Leeds will upload a list of patient identifiers (NHS numbers, date of birth, name and postcode) and a unique DEPICT study number to secure servers at NHS Digital for a cohort of children admitted to PICUs in England during a 3-year period (2014-16) – Dataset 1. Similarly, ICNARC will upload a similar list of patient identifiers and a unique local CMP identifier for children admitted to AICUs in England during the same 3-year period (2014-16) – Dataset 2. No clinical information will be transferred to NHS Digital. NHS Digital will first merge Dataset1 with Dataset 2. The merged dataset will then be linked to HES/ONS data. A pseudonymised dataset consisting of DEPICT study number, Unique CMP identifier, and HES/ONS data will be returned from NHS Digital to the University of Leicester. University of Leicester will send a list of DEPICT study numbers to University of Leeds and a list of unique CMP identifiers and corresponding DEPICTstudy numbers to ICNARC. University of Leeds will send PICANet clinical data to the University of Leicester. Similarly, ICNARC will send CMP clinical data to the University of Leicester. The final pseudonymised study dataset containing only the study number will be held at the University of Leicester for analysis. NHS Digital will follow established procedures to destroy patient identifiable data once the linkage has been completed.

The qualitative and questionnaire study raises ethical issues related to:

1. Patient/parent informed consent: Eligible patients and parents will be approached for consent to: a) complete questionnaires related to their experience of the transport; b) to be approached by a researcher for potential participation in an interview at a later date; c) to be approached by a researcher 12 months later for follow up quality of life questionnaire completion; and d) to consent for their child's PICANet data related to the transport and PICU admission to be

provided to the study team. Recognising that families of critically ill children are likely to be highly stressed during transport and their child's admission to intensive care, we will defer the consent approach to a suitable time after PICU admission as judged by the clinical team. We will ensure that experienced and qualified staff are involved in obtaining consent from the parents/families. Information sheets will be available in English as well as five other languages. Parents will be given as much time as required to consider whether they wish to participate in the study. It will be made clear to the parents that they will be free to withdraw their consent for their own and/or their child's participation in the study at any time without this having any impact on their child's care. The vast majority of children will be sedated and on a ventilator, therefore will be unable to remember their illness or transport experience. However, some children/young people may not be ventilated; we will provide them with age-appropriate information sheets and record their assent if they wish to participate. We will defer discussing the study with parents whose child dies in the PICU prior to consent being obtained in recognition of the parents' distress at that time. We will develop specific versions of study documents for bereaved parents.

2. Interviews: We recognise that recollecting a potentially difficult experience in their child's life may be upsetting for parents/families even if it is after several months. We will employ staff with previous experience of interviewing children/families on sensitive issues. Interviews will be structured over 1-2 hours with appropriate breaks if necessary. We will develop clear policies for support for families if required. It will be made clear to participants at the outset that the interview can be stopped at any time should they wish. Recognising that it can sometimes be difficult for participants to ask for an interview to be stopped, we will provide participants with a card or another agreed signal that they can use to indicate that they would like the interview to be stopped. This technique has been successfully employed in previous studies and participants have reported that knowing that they have a mechanism of stopping the interview has been reassuring and empowering should they want to do so.

   We will employ a range of creative methods to engage children/young people in interviews, including activities such as 'draw and write',[21] 'Talking mats',[22] and third-person craft activities, and a conversation will be developed around the use of these materials. Recognising that this is likely to have been a distressing time for children, the researcher will be particularly sensitive to, and careful about, how these experiences are explored. If children would like their parents to be present, this will be facilitated. Sessions are expected to last 30-60 minutes, to enable time for rapport building with children at the start of the session and some appropriate "ending" of the session before they leave. Members of the research team have experience of using creative methods and interviewing children, and any training in the use of specific methodologies will be provided to the researcher.

10 DATA MANAGEMENT

10.1 Source Documents

Source documents are original documents, data, and records from which participants' study data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence. All documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed consent, the participant will be referred to by the study participant number/code, not by name.

10.2 Direct Access to source data / documents

Only members of the study research team and authorised representatives from the sponsor will have direct access to the source data and study documentation. All source data and study documentation will also be available to external auditors if and when required, and inspectors in the event of regulatory inspection. Consent forms will be stored at local sites and patient identifiable data will not be shared outside the local site. Access to the final data set will remain with the chief investigator.

10.3 Data Recording and Record Keeping

The linked dataset for this study will not contain any patient identifiable data. These data will be held in secure servers at the University of Leicester. Access to the study dataset will be tightly managed by University of Leicester data access policies. Research staff working on the data will be employed at the University of Leicester.

Questionnaire data, including the 12-month follow up quality of life questionnaire data, will be collected and managed using REDCap electronic data capture tools hosted at University College London School of Life and Medical Sciences.[39] REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. Study participants will be identified by a unique study specific number in REDCap. The name and any other identifying detail will not be included in any study data electronic file. Thus, we will ensure that researchers undertaking the health economic evaluation and mathematical modelling will not have access to any patient identifiable information. Access to study data will be restricted to authorised individuals approved by the Chief Investigator employed at Great Ormond Street Hospital.

Interviews will be audio-recorded on an encrypted digital recorder (with consent/assent) and contemporaneous notes will be made by the researcher after each interview. On arrival back at

Great Ormond Street Hospital after completing an interview, the researcher will transfer all encrypted interviews to the secure server and securely delete the interview from the audio-recorder. Interviews will be transcribed verbatim using an external company (Take Note), with whom Great Ormond Street Hospital already have a contract with agreed terms and conditions to protect confidentiality. Names and any other identifying information (including hospital details, names of health professionals etc.) will be redacted in the transcript. All audio recordings, transcripts and notes will be stored on secure network folders at Great Ormond Street Hospital servers; access will be restricted to authorised users only. Study participants will be identified by a unique study specific number; the patient name or any other identifying detail will not be included in any study data electronic file.

10.4 Archiving

Archiving will be authorised by the Sponsor following submission of the end of study report. Essential documents will be retained for a **minimum** of 15 years after completion of the study. These documents will be retained for longer if required by the applicable regulatory requirements.

10.5 Research ethics approval

This protocol, patient information sheets, informed consent forms and other study-related documents will be reviewed and approved by the Sponsor and Research Ethics Committee with respect to scientific content and compliance with applicable research regulations involving human subjects.

11 PATIENT CONFIDENTIALITY & DATA PROTECTION

Patient identifiable data, including initials, date of birth and NHS/hospital number will be required for the registration process. The study staff will ensure that the participants' anonymity is maintained. The participants will be identified only by initials and a participant's ID number on the CRF and any electronic database. All documents will be stored securely at Great Ormond Street Hospital and only accessible by study staff and authorised personnel. The study will comply with the Data Protection Act, which requires data to be anonymised as soon as it is practical to do so. Data will be stored in a secure manner and in accordance with the Data Protection Act 1998.

12 FINANCIAL INFORMATION AND INSURANCE

This study is funded by the National Institute of Health Research Health Services Delivery Research program (NIHR HSDR ref: 15/136/45).

Cover for negligent harm will be provided by the Great Ormond Street Hospital for Children NHS Foundation Trust through the Clinical Negligent Scheme for Trusts (CNST).

13 DISSEMINATION

The results of the study will be disseminated actively and extensively. The research team has strong links with (a) the PICU community via the Paediatric Intensive Care Society (PICS), PICS Study Group (PICS-SG), and the NIHR CRN: Children Clinical Studies Group (CSG) in Anaesthesia, Intensive Care and Cardiology; (b) the PICU Transport community through the PICS Acute Transport Group; (c) the Healthcare Quality Improvement Partnership national audit programme through the Paediatric Intensive Care Audit Network (PICANet) and Intensive Care National Audit and Research Centre (ICNARC) Case Mix Programme; and (d) NHS England.

CLINICIANS AND ACADEMICS: Clinicians in the study steering committee will be drawn from all transport services in the UK, and will ensure wide dissemination of the results to frontline clinicians. The findings from our work will be presented at national and international conferences, potentially including the Annual Conference of the Royal College of Paediatrics and Child Health, the World Congress of Pediatric Intensive Care, PICS Annual Scientific Meeting, American Association of Pediatrics Conference, the European Society of Paediatric and Neonatal Intensive Care, and British Association of Critical Care Nurses (BACCN). A full report of the study will appear in the NIHR Health Services Delivery Journal. The study findings will also be published in high-impact, open-access, peer reviewed scientific journals and relevant professional journals.

POLICY MAKERS: Evidence to inform future clinical guidelines arising out of the research will be published and disseminated to professional societies concerned with the care of children presenting with acute illness, including PICS and the Royal College of Paediatrics and Child Health. Presentation slides will be prepared for use by the study team or others in disseminating the research findings.

PUBLIC: The results of the study will be disseminated to patients and their families, facilitated by the co-applicants, members of the research team who have links with PICS and the NIHR CSG, and via Family Groups we have liaised with already. A study website and links to social media will be created to publicise progress with the research and disseminate our findings.

14 PUBLICATIONS POLICY

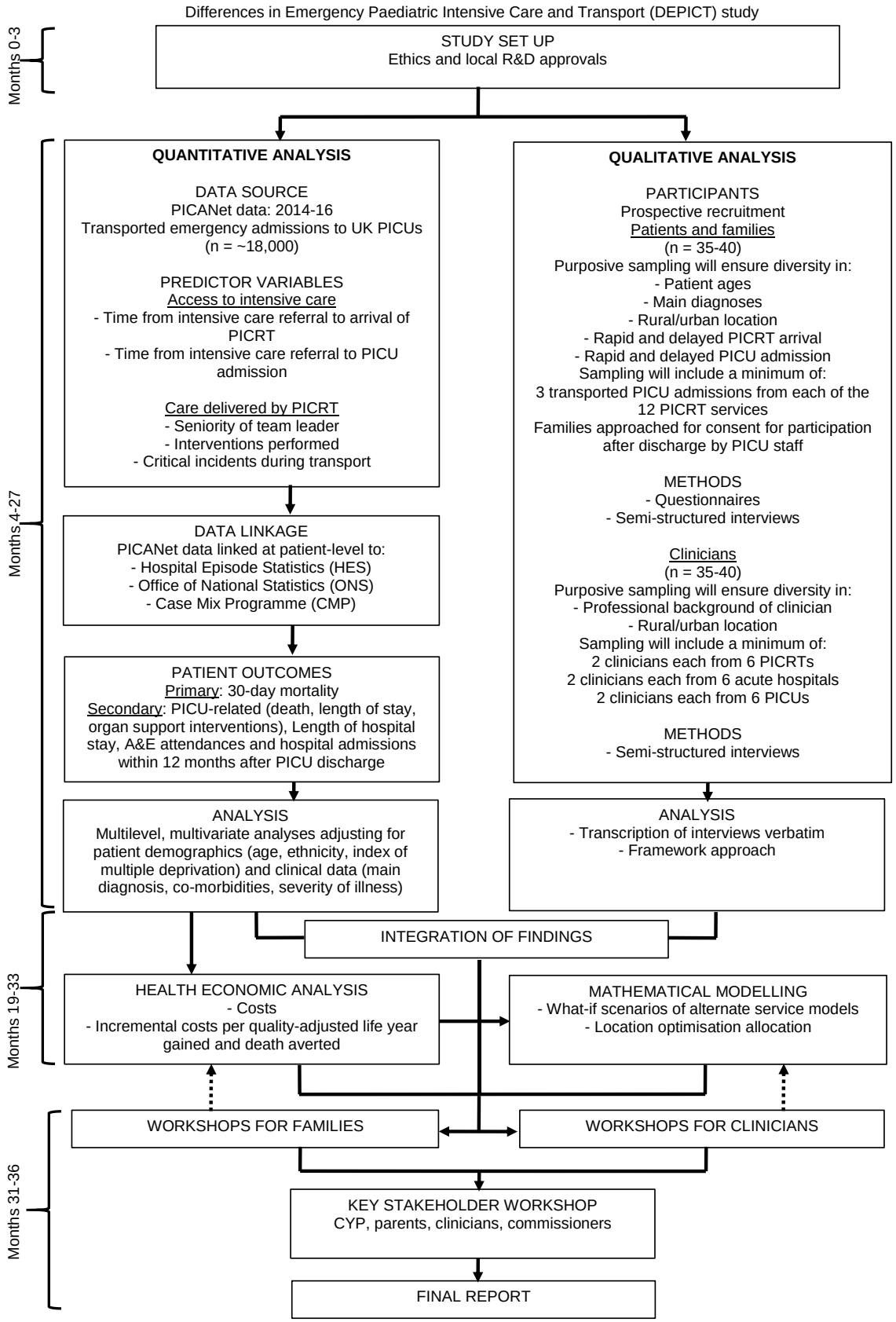
All individuals who have made substantial intellectual, scientific and practical contributions to the study and the manuscript will, where possible, will be credited as authors; all individuals credited as authors will deserve that designation. It is the responsibility of the Chief Investigator and co-PI and, ultimately, the Sponsor to ensure that these principles are upheld. The status of manuscripts in preparation will be reviewed by the Chief Investigator and Sponsor if required. In all cases where journal policies permit, all investigators who contribute patients to the study will be acknowledged.

15 REFERENCES

1. Viner RM, Hargreaves DS, Coffey C, Patton GC, Wolfe I. Deaths in young people aged 0-24 years in the UK compared with the EU15+ countries, 1970-2008: analysis of the WHO Mortality Database. Lancet. 2014;384(9946):880-92.
2. Pearson GA, Ward-Platt M, Harnden A, Kelly D. Why children die: avoidable factors associated with child deaths. Arch Dis Child. 2011;96(10):927-31.
3. Surgery in Children: are we there yet? National Confidential Enquiry into Patient Outcome and Death, 2011.
4. Metcalfe D, Bouamra O, Parsons NR, Aletrari MO, Lecky FE, Costa ML. Effect of regional trauma centralization on volume, injury severity and outcomes of injured patients admitted to trauma centres. The British journal of surgery. 2014;101(8):959-64.
5. Begg CB, Cramer LD, Hoskins WJ, Brennan MF. Impact of hospital volume on operative mortality for major cancer surgery. JAMA. 1998;280(20):1747-51.
6. Field D, Hodges S, Mason E, Burton P. Survival and place of treatment after premature delivery. Arch Dis Child. 1991;66(4 Spec No):408-10; discussion 10-1.
7. British Paediatric Association. The care of critically ill children. London: 1993.
8. Paediatric intensive care: A framework for the future. Wetherby: Department of Health, 1997.
9. Ramnarayan P, Polke E. The state of paediatric intensive care retrieval in Britain. Arch Dis Child. 2012;97(2):145-9.
10. Ramnarayan P, Thiru K, Parslow RC, Harrison DA, Draper ES, Rowan KM. Effect of specialist retrieval teams on outcomes in children admitted to paediatric intensive care units in England and Wales: a retrospective cohort study. Lancet. 2010;376(9742):698-704.
11. Paediatric Intensive Care Audit Network: Annual Report 2015 (published November 2015). Universities of Leeds and Leicester, 2015.
12. Colville G, Orr F, Gracey D. "The worst journey of our lives": parents' experiences of a specialised paediatric retrieval service. Intensive Crit Care Nurs. 2003;19(2):103-8.
13. Colville G, Darkins J, Hesketh J, Bennett V, Alcock J, Noyes J. The impact on parents of a child's admission to intensive care: integration of qualitative findings from a cross-sectional study. Intensive Crit Care Nurs. 2009;25(2):72-9.
14. Standards for the Care of Critically Ill Children: The Paediatric Intensive Society; 2010. 4th:[Available from: http://www.rcoa.ac.uk/docs/sccic_2010.pdf.
15. Department of Health. The Acutely or Critically Sick or Injured Child in the District General Hospital: A Team Response. London: 2006.
16. Brierley J, Carcillo JA, Choong K, Cornell T, Decaen A, Deymann A, et al. Clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock: 2007 update from the American College of Critical Care Medicine. Crit Care Med. 2009;37(2):666-88.
17. Kochanek PM, Carney N, Adelson PD, Ashwal S, Bell MJ, Bratton S, et al. Guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents--second edition. Pediatr Crit Care Med. 2012;13 Suppl 1:S1-82.

18. Colville GA, Gracey D. Mothers' recollections of the Paediatric Intensive Care Unit: associations with psychopathology and views on follow up. Intensive Crit Care Nurs. 2006;22(1):49-55.
19. Ramsay AI, Morris S, Hoffman A, Hunter RM, Boaden R, McKevitt C, et al. Effects of Centralizing Acute Stroke Services on Stroke Care Provision in Two Large Metropolitan Areas in England. Stroke. 2015;46(8):2244-51.
20. Paediatric Intensive Care Network (PICANet). National report of the Paediatric Intensive Care Audit Network, January 2011–December 2013. Leeds: 2014.
21. Horstman M, Aldiss S, Richardson A, Gibson F. Methodological issues when using the draw and write technique with children aged 6 to 12 years. Qual Health Res. 2008;18(7):1001-11.
22. Murphy J, Boa S. Using the WHO-ICF with talking mats to enable adults with long-term communication difficulties to participate in goal setting. Augment Altern Commun. 2012;28(1):52-60.
23. Guide to the methods of technology appraisal. National Institute for Health and Care Excellence (NICE), 2013.
24. Curtis LB, A. Unit Costs of Health and Social Care 2015. Personal Social Services Research Unit: University of Kent, 2015.
25. Horsman J, Furlong W, Feeny D, Torrance G. The Health Utilities Index (HUI): concepts, measurement properties and applications. Health and quality of life outcomes. 2003;1:54.
26. Khan KA, Petrou S, Rivero-Arias O, Walters SJ, Boyle SE. Mapping EQ-5D utility scores from the PedsQL generic core scales. Pharmacoeconomics. 2014;32(7):693-706.
27. Lacroix J, Hebert P, Fergusson D, Tinmouth A, Blajchman MA, Callum J, et al. The Age of Blood Evaluation (ABLE) randomized controlled trial: study design. Transfus Med Rev. 2011;25(3):197-205.
28. Investigators IT. Endovascular strategy or open repair for ruptured abdominal aortic aneurysm: one-year outcomes from the IMPROVE randomized trial. European heart journal. 2015;36(31):2061-9.
29. Barber J, Thompson S. Multiple regression of cost data: use of generalised linear models. J Health Serv Res Policy. 2004;9(4):197-204.
30. Kreif N, Grieve R, Sadique MZ. Statistical methods for cost-effectiveness analyses that use observational data: a critical appraisal tool and review of current practice. Health Econ. 2013;22(4):486-500.
31. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. Int J Technol Assess Health Care. 2013;29(2):117-22.
32. Knight VA, Harper PR, Smith L. Ambulance allocation for maximal survival with heterogeneous outcome measures. Omega. 2012;40(6):918-26.
33. Smith HK, Laporte G, Harper PR. Locational Analysis: Highlights of Growth to Maturity. The Journal of the Operational Research Society. 2009;60:s140-s8.
34. Batta R, Lejeune M, Prasad S. Public facility location using dispersion, population, and equity criteria. European Journal of Operational Research. 2014;234(3):819-29.
35. Larson RC. A hypercube queuing model for facility location and redistricting in urban emergency services. Computers & Operations Research. 1974;1(1):67-95.

16 Appendix A: Study Flow Chart



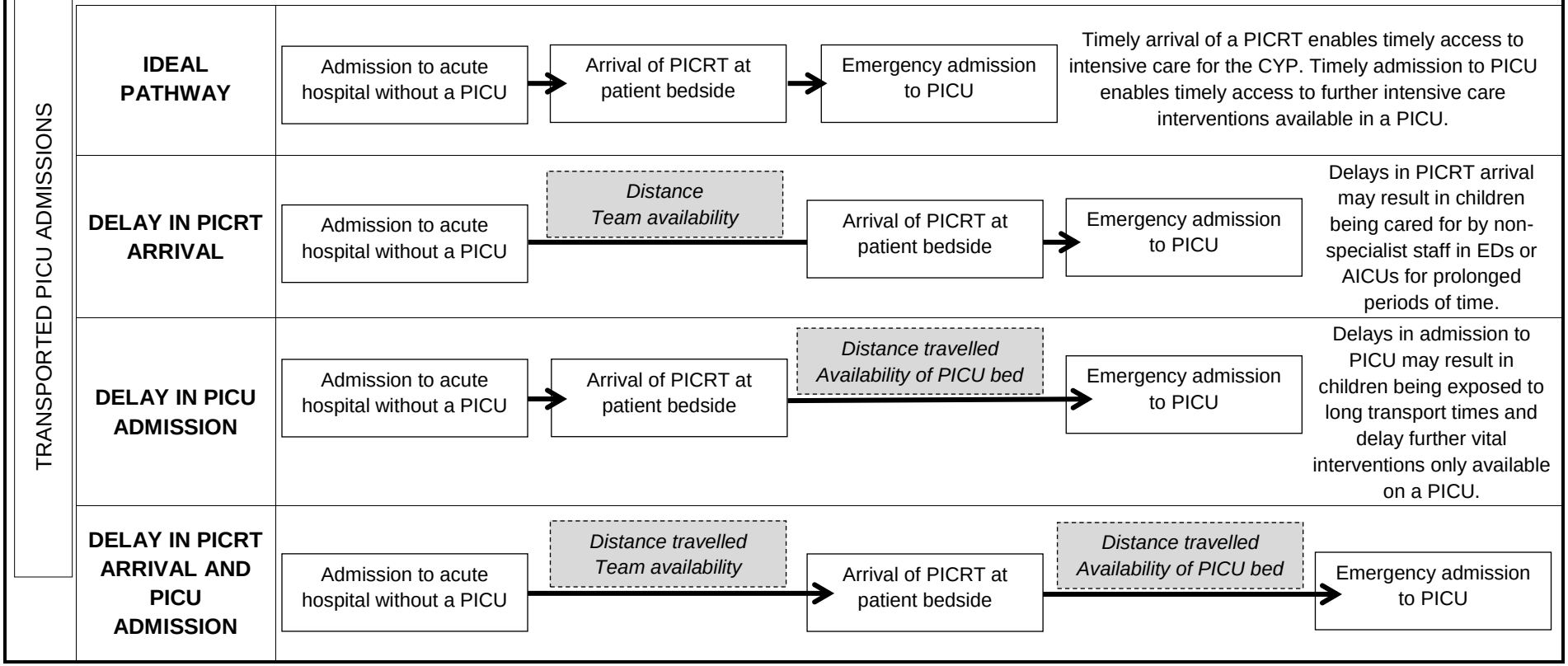
17 Appendix B: Example of patient pathway for a critically ill child requiring transport to a PICU

PANEL A: VARIATIONS IN THE TIMELINESS OF ACCESS TO EMERGENCY INTENSIVE CARE IN TRANSPORTED PICU ADMISSIONS

Critically ill/injured children who present to an acute hospital in the UK without a PICU require transport to a hospital with a PICU. Emergency intensive care is initiated by PICRTs and continued on PICU.

Shaded boxes represent factors that influence timeliness of access to emergency paediatric intensive care. PICRT team availability may vary by service (depending on how the service is organised and how many teams are available), geographical region (lengthy transports mean longer waits for a team to become available for the next transport), and season (a winter surge in demand for PICU/PICRT services mean that patients wait longer for a PICRT and/or travel a longer distance to a PICU bed).

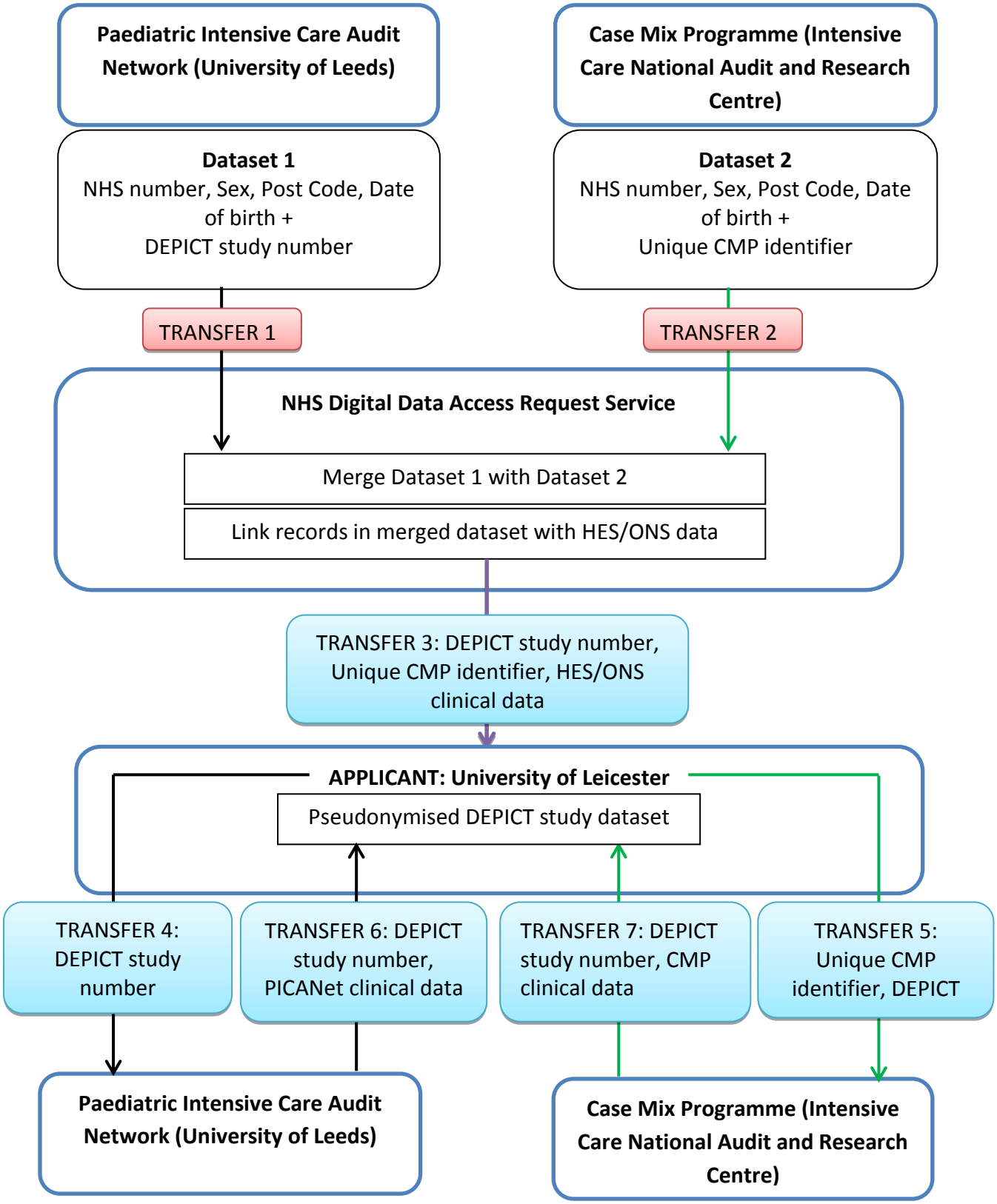
TRANSPORTED PICU ADMISSIONS



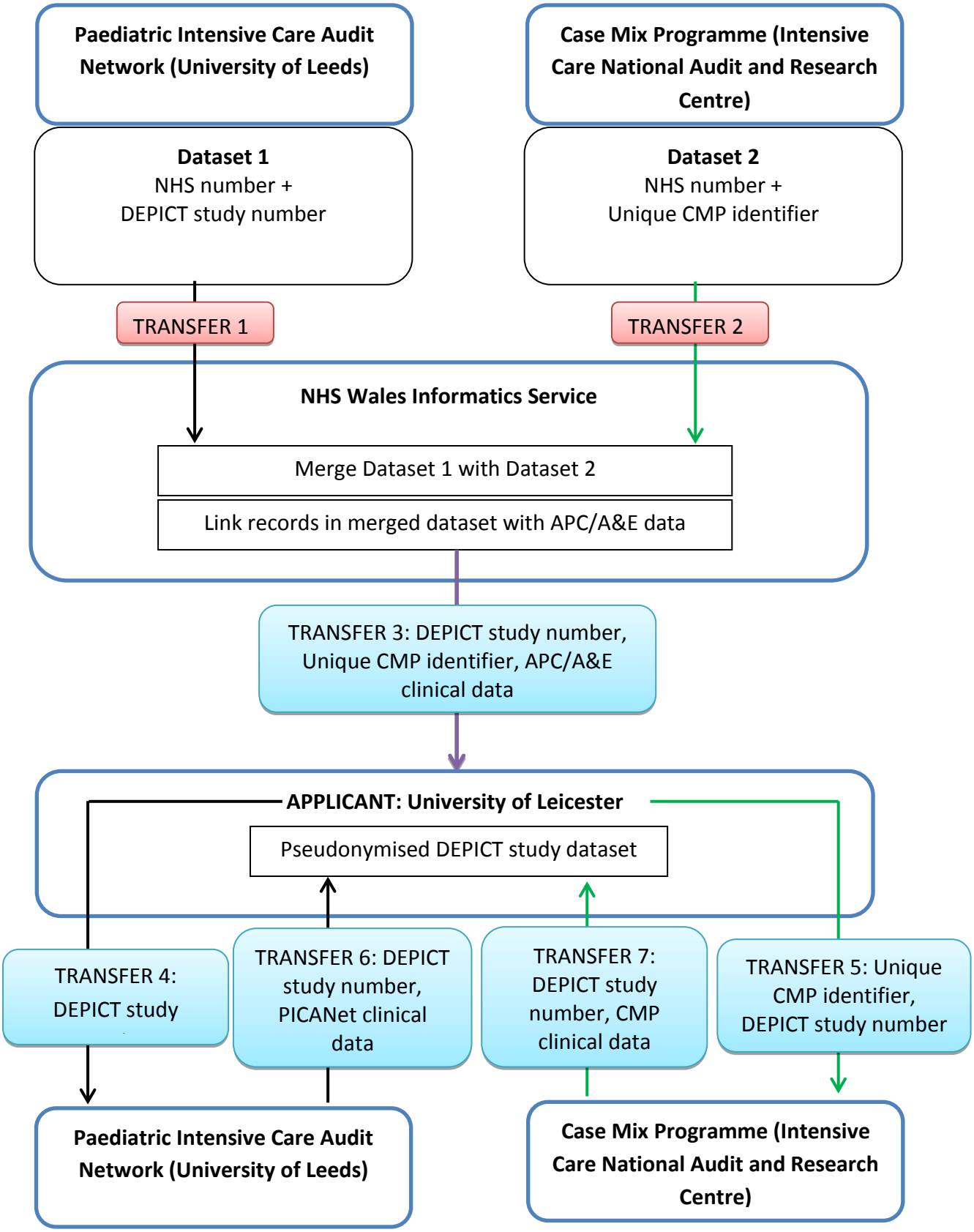
18 Appendix C: Data flow during linkage of data sources and generation of study dataset

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.

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



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



Appendix D: Schedule of Procedures (Qualitative and questionnaire study)

Procedures	PICU admission	2-3 months after PICU admission	Within 6 months of PICU admission	12 months after PICU admission
Informed consent for transport questionnaire completion, contact by GOSH qualitative researcher for interviews and completion of 12-month follow up questionnaires	x			
Transport questionnaire completion	x			
Contact by GOSH qualitative researcher for interviews		x		
Parent/children interviews			x	
Contact by researcher for 12-month follow up questionnaires				x
Completion of 12-month follow up questionnaires				x

20 Appendix E: Flow of data in the qualitative and questionnaire part of the study