Acute postnatal transfer and mortality in extremely preterm babies

Version 1.2
Date: 26/7/2016

SPONSOR: Imperial College London
SPONSOR REFERENCE: 16IC3460
FUNDER: Funded within a MRC fellowship awarded to Dr C Gale (MR/N008405/1)
STUDY CO-ORDINATION: Neonatal Medicine Research Group, Imperial College London, Chelsea and Westminster Hospital campus
IRAS project ID: 209090
REC Reference: 16/EM/0351
Study Group

Chief Investigator: Dr Christopher Gale

Co-investigators: Dr Kjell Helenius, Professor Neena Modi, Professor Liisa Lehtonen

Statistician: Dr Nicholas Longford

Sponsor

Imperial College London; for further information regarding sponsorship conditions, please contact the Head of Regulatory Compliance at:

Joint Research Compliance Office
Imperial College London & Imperial College Healthcare NHS Trust
2nd Floor Medical School Building
St Mary’s Hospital
Praed Street
London
W2 1NY
Tel: 020759 41862

This protocol describes a study entitled “Acute postnatal transfer and mortality in extremely preterm babies” and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the NHS Research Governance Framework for Health and Social Care (2nd edition). It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.
## GLOSSARY OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>BPD</td>
<td>Bronchopulmonary dysplasia</td>
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<td>IVH</td>
<td>Intraventricular haemorrhage</td>
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<td>MRC</td>
<td>Medical Research Council</td>
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<td>NHS</td>
<td>National Health Service</td>
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<td>NNRD</td>
<td>National Neonatal Research Database</td>
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<td>NEC</td>
<td>Necrotising enterocolitis</td>
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<td>NDAU</td>
<td>Neonatal Data Analysis Unit</td>
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<td>NICU</td>
<td>Neonatal Intensive Care Unit</td>
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<tr>
<td>PVH</td>
<td>Periventricular haemorrhage</td>
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<td>ROP</td>
<td>Retinopathy of prematurity</td>
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<td>UK</td>
<td>United Kingdom</td>
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STUDY SUMMARY

TITLE Acute postnatal transfer and mortality in extremely preterm babies

DESIGN Register-based epidemiological study using anonymised data

AIMS To determine the impact of acute postnatal transfer (within 48 hours of birth) on mortality and morbidity among extremely preterm infants

OUTCOME MEASURES Primary: death

Secondary: intraventricular/periventricular haemorrhage, length of stay, composite outcome of death or prematurity-related morbidities

POPULATION Infants born in England, Wales and Scotland at less than 28 gestational weeks

ELIGIBILITY All infants born at less than 28 gestational weeks, who are registered in the National Neonatal Research Database (NNRD).

DURATION Retrospective, non-identifiable data held in a pre-existing research database (the NNRD) on infants born between 2009-2015 will be used.

KEYWORDS Transfer, preterm, infant, mortality, matching

1. INTRODUCTION

1.1 BACKGROUND

Neonatal specialist care, and in particular the high intensity care required by the most preterm babies, is an expensive, low volume service that is not available at all neonatal units. As preterm birth is often precipitate and unplanned, the postnatal transfer of infants delivered at smaller neonatal units but requiring specialist care is unavoidable. In England in 2009-2010 over one third of 27-28 week gestation babies were transferred in the first 28 days following birth, and despite nationwide attempts at reduction, the rate of postnatal transfer is increasing. Due to the unpredictable nature of preterm birth many acute postnatal transfers are unavoidable, and where specialist care is not available at the local neonatal unit, both justified and desirable. Increasingly however acute postnatal transfer of preterm babies is undertaken for reasons such as inadequate cot capacity at the unit of delivery. In 2008-2009 25% of all transfers undertaken in the first 24 hours among 27 to 28 week gestation babies were to units providing equivalent levels of neonatal care. The Bliss report on neonatal transfers (2016) showed that in the UK each year about 1000 newborn transfers take place for reasons other than medical need.
1.2 RATIONALE FOR CURRENT STUDY

The acute postnatal transfer of preterm babies is a complex and often difficult undertaking; previous studies have demonstrated an association with mortality and morbidity (5-9). However, the relevance of these studies is limited by three factors. First, the majority of studies were carried out prior to the widespread use of antenatal steroids, surfactant, and specialist neonatal transport services. Second, infants undergoing acute transfer tend to be more unwell than the “control” group not undergoing transfer (4), and therefore any association may have represented confounding by indication. Third, because babies in the transferred group were moved from less specialised to more specialised neonatal units, and initial management practice may be different between them, these studies have been unable to separate the association of adverse outcomes and acute postnatal transfer from the association of adverse outcomes and initial management at less specialised units.

This study will compare 4 groups of infants; i) those transferred between hospitals with equal levels of neonatal care (horizontal transfers); ii) those transferred from a lower level of care to a higher level of care (upward vertical transfers); iii) those transferred from a higher level of care to a lower level of care (downward vertical transfers) and iv) infants born in a tertiary hospital and not transferred (no transfer). This will enable us to separate out the impact of stabilisation at a lower intensity neonatal unit from the impact of postnatal transfer.

2. STUDY OBJECTIVES

The primary objective of this study is to examine the effect of postnatal transfer on mortality in a contemporary, national population cohort and to control for the effects of initial management. Secondary objectives are to examine possible effects of postnatal transfer on major morbidity and length of stay.

2.1 HYPOTHESIS

Among extremely preterm infants, acute postnatal transfer is associated with mortality and major prematurity related morbidities. This association persists after controlling for resuscitation and initial management at a lower volume unit.

3. STUDY DESIGN

The study is an epidemiological, register-based study. Subjects are very preterm infants born below 28 gestational weeks in England, Scotland and Wales at a NHS neonatal unit that contributes data to the NNRD. The estimated number if infants is 18,000, of which approximately 400 have undergone horizontal transfer for cot capacity/staffing reasons.

All analysis will be using anonymised data held in an approved research database, the NNRD. No patient identifiable information will be used in this study.

3.1 STUDY OUTCOME MEASURES

The primary outcome measure is mortality.
Secondary outcome measures:
- Major prematurity-related morbidities (including intraventricular/periventricular haemorrhage (IVH/PVH), necrotising enterocolitis ( NEC), retinopathy of prematurity (ROP), bronchopulmonary dysplasia (BPD))
- Length of stay

4. PARTICIPANT ENTRY

4.1 INCLUSION CRITERIA
There will be no active recruitment of patients as this is an epidemiological study using routinely recorded, anonymised data held within an established research database, the NNRD.

4.2 EXCLUSION CRITERIA
There are no exclusion criteria.

5. ASSESSMENT AND FOLLOW-UP
There will be no assessment or follow-up.

6. DATA ANALYSIS
Anonymised data held within the NNRD will be used for this study.

Analyses will compare outcomes in the following groups of infants:
- Infants transferred to an equivalent level unit in the first 48 hours (Horizontal transfer)
- Infants transferred to a higher level unit in the first 48 hours (Upwards vertical transfer)
- Infants who are not transferred in the first 48 hours
- Infants transferred from a higher level unit to a lower level unit in the first 48 hours (Downwards vertical transfer)

To control for confounding by indication three approaches will be applied:
1. LOGISTIC REGRESSION: Logistic regression models will be used to adjust for factors and with potential to impact outcome measures. These will include gestational age, birth weight, maternal illnesses, antenatal steroid administration, multiple birth, infant sex.
2. MATCHING: Infants will be matched between groups on the following factors: infant sex, birthweight, gestational age at birth, multiple birth (yes/no), maternal complete course of antenatal steroids (yes/no) using propensity scoring or a similar method for forming matched groups.
3. INSTRUMENTAL VARIABLE: Instruments will be developed that are correlated i) with transfer and ii) with horizontal transfer specifically. An instrumental variable approach will be used to limit confounding by indication, and to separate the influence of initial treatment from the postnatal transfer itself.
Potential instruments include:
- “distance from home address to a low level neonatal unit”: the closer a mother’s place of residence is to a lower level neonatal unit, the more likely they are to need acute postnatal transfer to a higher level unit following extremely preterm delivery.
“distance from home address to a neonatal unit with high horizontal transfer rate”: the closer a mother’s place of residence is to a neonatal unit with high rates of acute horizontal transfer, the more likely an infant is to need acute horizontal transfer following extremely preterm delivery.

7. REGULATORY ISSUES

7.1 ETHICS APPROVAL
NHS Research Ethics Committee and HRA approvals will be gained before the study commences.

7.2 CONSENT
This study will only use anonymised data held in an established research database, the NNRD.

7.3 CONFIDENTIALITY
Only anonymised data will be used in this study.

7.4 INDEMNITY
Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study.

7.5 SPONSOR
Imperial College London

7.6 FUNDING
The study is funded through a MRC fellowship awarded to Dr. Chris Gale.

9. STUDY MANAGEMENT
The day-to-day management of the study will be co-ordinated through the Neonatal Medicine Research group at Imperial College London

10. REFERENCES