SHORT-TERM OUTCOMES OF INBORN VS OUTBORN VERY LOW BIRTHWEIGHT NEONATES (< 1500 G) IN THE GROOTE SCHUUR NEONATAL NURSERY

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Date: 9 February 2016
I would like to express my gratitude to:

Professor Michael Harrison, my supervisor, for your mentorship, patience and for never letting me forget to wash my hands.

The Groote Schuur Nursery family – the doctors, sisters and allied team – for the privilege to learn under your guidance, and for your unwavering commitment to caring for our tiny patients.
DEDICATION

To my daughter, Charlotte,

Dare to dream the biggest dreams and aim for the brightest stars. I hope that I can lead by example.
TABLE OF CONTENTS

Declaration i
Acknowledgements ii
Dedication ii
Abbreviations 1
Abstract 2

Literature Review
  Search strategy 3
  Inclusion and Exclusion Criteria 5
  Introduction 6
  Perinatal Regionalisation 7
  Maternal Characteristics 9
  Infant Characteristics 10
  Outcomes 11

Study Design
  Objectives of Study 13
  Method 13
  Confidentiality 14
  Informed Consent 14
  Ethics 14
  Data Analysis 14
  Limitations 15
  Definitions of Parameters 16
Results

Study Cohort

Maternal Characteristics
- Antenatal care
- Antenatal steroids
- Hypertension
- Chorioamnionitis
- Caesarean section

Infant Characteristics
- Ventilatory support
- Surfactant administration
- Hypothermia on admission

Outcomes
- Late infection
- Necrotising enterocolitis
- Severe intraventricular haemorrhage
- Chronic lung disease
- Survival without morbidity
- Mortality

Table: Summary of Results

Discussion

Conclusion and Recommendations

References

Appendix A: VON Data Capture Form

Appendix B: Ethics Approval

Appendix C: Turnitin Report
CLD – Chronic Lung Disease
CPAP – Continuous Positive Airway Pressure
ELBW – Extremely Low Birth Weight (1000g and less)
HFOV – High Frequency Oscillatory Ventilation
GSH – Groote Schuur Hospital
IPPV – Intermittent Positive Pressure Ventilation
IVH – Intraventricular Haemorrhage
MOU – Midwife Obstetric Unit
NEC – Necrotising Enterocolitis
VLBW - Very Low Birth Weight (1500g and less)
VON – Vermont Oxford Network
ABSTRACT

Background: The Groote Schuur Neonatal Nursery provides Level 3 care for the Metro West Health District in the Western Cape, South Africa. Worldwide, Very Low Birth Weight (VLBW) neonates have improved outcomes when delivered in Level 3 neonatal units, compared with those who are transported from other facilities.

Objectives: Identify the characteristics of the neonates admitted to the Groote Schuur Neonatal Nursery, with emphasis on the differences between inborn and outborn patients. Compare the clinical outcomes between these 2 groups and identify focus areas for improvement of outcomes for our patients.

Methods: A retrospective cohort study. Neonates weighing 1500g and less admitted to the Groote Schuur Hospital (GSH) Neonatal Nursery between 1 January 2012 and 31 December 2013 and enrolled on the Vermont Oxford Network database were reviewed. Maternal and infant characteristics, as well as outcomes at the time of discharge from hospital were analysed.

Results: A total of 1032 VLBW neonates were enrolled. 906 (87.8%) were delivered at GSH, and 126 (12.2%) were outborn and transported to our facility.

Access to antenatal care, antenatal steroids and inborn status were statistically significant predictors for mortality and survival without morbidity. The mothers of inborn patients were more likely to have received antenatal care (89.1% vs 57.9%, p <0.0001) and antenatal steroids (64.2% vs 15.2%, p <0.0001).

Inborns were less likely to require ventilatory support (16.2% vs 57.9%, p <0.0001) and surfactant administration (25.3% vs 65.1%, p <0.0001).

The inborn cohort had a lower incidence of late infection (8.8% vs 23.4%, p <0.0001), severe intraventricular haemorrhage (3.7% vs 13.9%, p <0.0001) and chronic lung disease (5.3% vs 13.4%, p =0.003). The incidence of necrotising enterocolitis was similar between the two groups (5.9% vs 8.7%, p =0.227).

18.4% of inborns and 33.3% of outborns demised (p <0.0001), mostly on the first 2 days of admission. Mortality declined as birth weight increased. Of the survivors, 83.5% of inborns and 70.2% of outborns did not develop serious morbidity (p =0.003).

Significant morbidity and mortality was noted in the outborn group weighing 800g and less, with only one outborn patient in the cohort surviving to discharge without major morbidity.

Conclusion: VLBW neonates delivered at Groote Schuur Hospital had better outcomes compared with their outborn counterparts. Perinatal regionalisation was found to be beneficial to our patients, with antenatal care, timeous in-utero transfer and antenatal steroids contributing to excellent outcomes.
LITERATURE REVIEW

Search strategy

The Groote Schuur Neonatal Nursery admits over 500 Very Low Birth Weight (VLBW) premature neonates, weighing 1500g and less, every year. Many of these are referred from other centres within the Metro West district and beyond. Over the past few decades, the quality of care of premature neonates has improved significantly worldwide, with access to specialised services and resources through regionalisation of care impacting those particularly at risk. It is also recognised that those who are born outside of specialist centres, referred to as “outborns”, fare worse.

The objective of this literature review was to establish the differences between inborn and outborn premature VLBW neonates, with emphasis on the following parameters:

Maternal characteristics:
- Antenatal care
- Antenatal steroids
- Hypertension
- Chorioamnionitis
- Caesarean section

Infant characteristics:
- Ventilatory support
- Surfactant administration
- Hypothermia on admission

Outcomes:
- Late infection
- Necrotising enterocolitis
- Severe intraventricular haemorrhage
- Chronic lung disease
- Mean length of admission
- Survival with serious morbidity
- Mortality

A search of the relevant literature was undertaken on 12 January 2015 using the PubMed database. All article types were included, and studies were limited to those published since 1990. Full texts were downloaded via the UCT Library website.

The yield of the search was as follows:
Search 1: "Outborn" and "Very Low Birth Weight"

44 articles

Inclusion and exclusion criteria applied based on titles, and duplicates excluded

42 articles

Search 2: "Premature" and "Outborn" and "Outcomes"

29 articles

Search 3: "Perinatal Regionalisation" and "Very Low Birth Weight"

11 articles

Inclusion and exclusion criteria applied to full text articles

30 articles reviewed
Inclusion criteria

- Human subjects
- Patients enrolled in the neonatal period, i.e. first 28 days of life
- Very Low Birth Weight patients i.e. weighing less than 1500g
  - Studies of Extremely Low Birth Weight neonates (less than 1000g) were also included
- Comparison of patients born within tertiary centers (inborns) to those delivered outside of tertiary centers (outborns)
- Transport of patients to tertiary centers
- Short term outcome only i.e. up to the point of discharge from the initial hospital admission
- Full text in English

Exclusion criteria

- Patients enrolled beyond the neonatal period
- Cohorts of patients weighing over 1500g
- Intervention studies of therapies not offered within our unit
- Studies describing surgical / operative interventions
- Long-term outcomes, such as neurodevelopmental studies
- Genetic studies
- Extreme prematurity at the limits of viability
- Pre-surfactant era studies (i.e. before 1990)

30 full text articles were reviewed and the salient points summarized. All studies were peer reviewed.

18 of the studies were conducted in North America (11 in the USA, one of which included a European cohort, and 7 in Canada). 4 studies were conducted in Asia and the Middle East respectively, 2 in Europe and 1 in Australia. One of the articles analysed was a metanalysis of the literature between 1976 and 2010. No studies published in Africa were found during the search.

The literature search was repeated on 10 November 2015. One additional article meeting inclusion criteria, published in China, was added to the review.
INTRODUCTION

The Groot Schuur Neonatal Nursery, with its 75-bed capacity, admits over 2000 neonates per year. Over 500 of these are Very Low Birth Weight infants, who spend a long period of time in the Unit. The Neonatal Nursery offers Intensive Care facilities, with 8 beds for conventional and oscillatory ventilation, 12 beds with non-invasive ventilatory facilities, and a 10-bed Kangaroo Mother Care facility. The rest of the unit provides High Care for growing premature neonates.

Groote Schuur Hospital and Tygerberg Hospital are the only Level 3 neonatal units within the Cape Town Metro District, and thus provide care over a large geographical area. (See Image 1)

The Groote Schuur Hospital Neonatal Nursery serves the Western, Southern, Klipfontein, Mitchells Plain and Khayelitsha Health sub-districts – collectively termed the Metro West. Level 2 care is provided by Mowbray Maternity Hospital and New Somerset Hospital, and Level 1 care by several Midwife Obstetric Units (MOU’s) and District Hospitals. George Hospital, several hundred kilometers away, also falls under the University of Cape Town academic service, and thus some complex patients are referred to Cape Town for care.

The Tygerberg Hospital Neonatal Nursery serves the Northern, Eastern and Tygerberg health sub-districts – collectively termed the Metro East.

Image 1. Cape Town Metro Health Sub-Districts
Prior to May 2012 the place of delivery was based on maternal condition, resulting in many neonates requiring tertiary care being delivered by low-risk mothers in Level 1 and 2 settings.

The new policy stipulates that threatened preterm deliveries at 26 – 30 weeks, or expected birth weight of 700g – 1200g be transferred to the perinatal service at Groote Schuur Hospital. Although in-utero transfer is preferred, neonates delivered at Midwife Obstetric Units (MOU’s) within the referral network weighing 700g – 1200g should also be transferred to the GSH nursery. Deliveries less than 700g or 26 weeks are discussed with the consultant prior to transfer, and those anticipated to be at least 30 weeks’ gestation or weighing 1200g or more are referred to Level 2 hospitals.

Outborns tend to be less mature and more ill than their inborn counterparts. It is recognised that optimising maternal conditions, intrauterine transfer and delivery at Level 3 centres contributes to improved perinatal outcomes for premature neonates. Based on the literature, the place of delivery policy in the Metro West Health District in the Western Cape, South Africa, was revised and implemented in May 2012.

**PERINATAL REGIONALISATION**

The concept of perinatal regionalisation was initially developed in 1976, with an aim to identify and provide appropriate care for high-risk pregnancies. Through comprehensive assessment of maternal and foetal factors, the most appropriate location of delivery could be determined, with provision of relevant technology and services. By identifying the demands of low- to high-risk deliveries, appropriate infrastructure could be put into place.

Level 1 facilities are equipped to provide basic care for low-risk deliveries, healthy term neonates and to administer routine postnatal care. Level 2 facilities aim to provide specialised care to ill neonates over 32 weeks’ gestation and weighing over 1500g, or those recovering from ICU admissions. Ventilation can be provided for short periods of time. Internationally, Level 3 subspecialty facilities are divided into 3A, aimed for neonates over 28 weeks’ gestation and weighing over 1000g, 3B, catering for those less than 28 weeks’ gestation, weighing less than 1000g and requiring advanced respiratory support and subspecialist care, and 3C, where extracorporeal life support and cardiac surgery is offered on-site.
Australia and Canada, with their vast geographical areas, have established successful regionalisation of services\(^1,\,4\). Significant variations have been documented in the USA\(^2,\,5\) and Italy\(^6\), whereas post-delivery transfer of premature neonates is commonplace in Asia\(^7,\,8\). Patients admitted to specialised neonatal units fare better than those admitted to freestanding paediatric hospitals where, despite skilled services, they are more likely to have surgical problems, congenital cardiac lesions and metabolic abnormalities and therefore have poorer outcomes\(^9\). No literature exists on regionalisation of services for premature neonates in the African setting.

In Australia, Lui et al demonstrated a 25% reduction in outborn deliveries of preterm infants between 23 and 28 weeks’ gestation after implementation of a regionalisation policy. A 14% reduction in outborn mortality was also noted, likely due to an increased number of mothers receiving prenatal steroids, as well as the formation of a specialised neonatal transfer team\(^4\). In this study, only half of the outborn premature neonates were offered Neonatal Intensive Care Unit (NICU) care, compared with almost all of those delivered within a Level 3 unit. Furthermore, the outborn group may have been biased, containing only those who were robust enough for transfer\(^4\). Those who weren’t transferred almost certainly died, as no resources for their care were available in the peripheries\(^4\).

The initial resuscitation and stabilisation of preterm neonates after delivery impacts their morbidity and mortality\(^5\), and it is suggested that some outborn preterm infants die shortly after delivery or before transport can be arranged to a Level 3 facility\(^10\). Those who are transported by less experienced teams and over greater distances have also been found to have poorer physiological outcomes\(^11\).

Gestational age is strong predictor of outcome\(^9,\,12,\,13\), and it has been suggested that the benefit of inborn status is greatest for those neonates with a gestational age of 29 weeks and less\(^12\).
MATERNAL CHARACTERISTICS

ANTENATAL CARE AND STEROIDS

Chien et al demonstrated that more mothers of inborn VLBW neonates received prenatal care and steroids \(^1\). Mothers delivering at Level 3 facilities were noted to have a higher incidence of pre-existing comorbidities, such as hypertension, and more pregnancy-related complications \(^5,14\). These findings are in keeping with the fact that high-risk pregnancies should be delivered at Level 3 centres.

Maternal social and behavioural factors also play a role in location of delivery \(^10\). A lack of antenatal steroids has been associated with a lack of prenatal care and outborn status \(^14\), all of which were statistically significant factors contributing towards mortality in the study by Moro et al \(^15\).

Antenatal steroids are protective against chronic lung disease and severe intraventricular haemorrhage \(^16\), but are not associated with an increased risk of late sepsis \(^17\). The administration of antenatal steroids seems to be of more significance than outborn status itself \(^18\) and can be an independent predictor of outcome \(^19\). When corrected for in a study on patients with severe IVH, place of delivery was no longer significant, suggesting that more at-risk mothers are less likely to have received steroids \(^18\).

CAESAREAN SECTION

Vaginal delivery has been associated with increased risk of severe intraventricular haemorrhage \(^13,20,21\), with a particularly poor outcome for those neonates weighing 750 grams and less \(^20\). The negative impact of vaginal delivery decreases as the birth weight increases \(^20\). A higher incidence of delivery by caesarean section was noted in the inborn population in a Canadian cohort \(^1\), in keeping with the fact that high-risk pregnancies are delivered at level 3 units.
INFANT CHARACTERISTICS

VENTILATORY SUPPORT

Ventilation strategies vary across regions, and Levesque et al noted a 50% reduction in chronic lung disease, as well as a decreased incidence of adverse events such as hypotension, and less surfactant and oxygen requirements when non-invasive continuous positive airway pressure (CPAP) ventilation was made the mainstay of care, with strict intubation and extubation criteria for mechanical ventilation. Outborns were excluded from this study, and a small sample size rendered the results not statistically significant. Those who developed chronic lung disease tended to have received prolonged mechanical ventilation.

Mechanical ventilation has also been implicated in increased risk of severe intraventricular haemorrhage and nosocomial sepsis.

SURFACTANT ADMINISTRATION

Mortality in VLBW neonates has decreased since the introduction of exogenous surfactant in 1990.

In a prospective Israeli study pre-transfer surfactant was administered, in addition to skilled resuscitation, and no difference in severe IVH or chronic lung disease was noted between the inborn and outborn groups. A small study in the USA in the early 1990’s also noted no difference in outcomes in outborns who received pre-transfer surfactant and their inborn counterparts. Surfactant administration on the first day of life was a marker of poor outcome in a recent Canadian study.

HYPOTHERMIA ON ADMISSION

A Malaysian study observed that 32% of inborn and 41% of outborns were hypothermic, with a skin temperature of less than 36 degrees Celsius, on admission. These neonates were at a higher risk of hypotension and death, particularly in the outborn group.

A recent Chinese study demonstrated that the incidence of hypothermia can be reduced by implementing simple interventions such as increasing the temperature in the delivery room, pre-warming incubators prior to delivery, and education of resuscitation and transport teams. A decline in hypothermia was associated with a statistically significant decrease in mortality in VLBW neonates.
OUTCOMES

LATE INFECTION

In a Canadian study, 23% of VLBW neonates in the network developed sepsis, 95% of which was nosocomial. Risk factors included a gestational age of 29 weeks and less, outborn status, mechanical ventilation and parenteral nutrition. A higher risk of nosocomial sepsis was noted in neonates admitted to freestanding paediatric hospitals as opposed to Level 3 neonatal units.

NECROTISING ENTEROCOLITIS

Necrotising enterocolitis, with its implications for mortality and adverse developmental outcomes, was noted to be more prevalent in the outborn group in the Australian study by Lui et al. This declined over the duration of the study, likely as a result of improved perinatal regionalisation and increased access to prenatal steroids by outborn mothers.

No difference in NEC incidence between inborns and outborns was noted in a relatively small Taiwanese cohort.

SEVERE INTRAVENTRICULAR HAEMORRHAGE

An increased risk of severe intraventricular haemorrhage (IVH) has been noted in transported infants, with those less than 26 weeks at the highest risk. Outborn status itself was not a significant predictive factor on multivariate analysis, but antenatal steroids, vaginal delivery, 5 minute Apgar score and gestational age were found to be risk factors.

CHRONIC LUNG DISEASE

Outborns have been found to experience an increased incidence of chronic lung disease in some studies, with an odds ratio of 1.70 noted in those between 27 and 29 weeks compared with their inborn counterparts in Canada. No statistically significant difference was noted in outborns who had access to full resuscitation, ventilation and surfactant at their referring hospital, and no difference was noted in the NEOPAIN trial across the USA and Europe.
SURVIVAL WITHOUT MORBIDITY

A lower mortality rate was observed in outborn neonates in an Israeli study, but at the cost of a higher incidence of brain damage due to severe intraventricular haemorrhage \(^{30}\).

In a Canadian study enrolling over 6000 premature neonates, 37% survived without serious morbidities. Predictors for morbidity included lower gestational age, physiological condition on admission, outborn status, prenatal steroids, ventilatory support and surfactant administration on day 1 of life \(^{19}\).

MORTALITY

Mortality is an extensively studied outcome in outborn very low birth weight (VLBW) neonates, with odds ratios varying between 1.20 \(^{6}\) and 2.28 \(^{2}\) of dying compared with their inborn counterparts.

A study in Missouri, USA, comparing the early 1980’s and 1990’s, demonstrated an increase in level 2 and 3 deliveries, but only an appreciable decline (42.5%) in neonatal mortality of VLBW neonates in those delivered in level 3 units \(^{2}\).

In Italy, despite a large number of Level 3 units (125 units countrywide, with median admissions of 34 patients per unit per year) less perinatal centralisation and more outborn deliveries of VLBW neonates were noted in the South compared with the North. The mortalities between the regions differed significantly: 15.6% in the North and 23.4% in the South, with an adjusted relative risk of mortality of 1.48. Outborns fared poorly, with a relative risk of 1.20 of mortality compared with inborns \(^{6}\).

A meta-analysis of literature between 1976 and 2010, with a total study population of 104 944 patients showed an overall odds ratio of 1.62 of mortality for VLBW neonates born outside of Level 3 facilities. When the analysis was restricted to 9 high-quality articles, enrolling a total of 46 318 patients, a 60% increase in the odds of mortality was still demonstrated in the outborn population. 5 studies documenting the mortality of ELBW neonates, weighing less than 1000g, were combined (\(n = 13\) 093), and showed an 80% increased risk of mortality in outborns. Despite the 35 year span of the analysis, the association between place of delivery and mortality did not change over time \(^{31}\).
STUDY DESIGN

OBJECTIVES OF STUDY

1. Identify the characteristics of the neonates admitted to the Groote Schuur Neonatal Nursery, with emphasis on the differences between inborn and outborn patients
2. Compare the clinical outcomes between inborn and outborn patients
3. Identify focus areas for improvement of outcomes for our patients

METHOD

A retrospective cohort study of neonates weighing 1500g and less admitted to the Groote Schuur Neonatal Nursery between 1 January 2012 and 31 December 2013, and subsequently enrolled in the Vermont Oxford Network (VON) Database. A database analysis was performed.

Inclusion criteria:

- Very Low Birth Weight and Extremely Low Birth Weight neonates \(\text{i.e. those weighing 1500g and less at birth}\)
- Patients admitted during the neonatal period \(\text{i.e.: first 28 days of life}\)
- VLBW neonates delivered at Groote Schuur Hospital \(\text{(referred to as inborns)}\) as well as those born at any other facility, including those beyond the realms of the Metro West Health District \(\text{(referred to as outborns)}\)

Exclusion criteria:

- All patients weighing more than 1500g at birth
- Patients admitted beyond the neonatal period \(\text{i.e.: 29 days and older}\)

Data were collected prospectively using the VON data capture form, and stored on the VON database. Definitions used are based on those specified by the VON database.

The VON database comprises over a thousand neonatal units worldwide, with over 1.5 million VLBW neonates enrolled. Established in 1988, this non-profit organization aims to improve the quality of care of premature neonates through research and quality improvement projects. The GSH Neonatal Nursery became a member in 2012, and submits data on over 500 patients per year. Data from patients are collected by medical officers and registrars working in the unit by means of a standardized data collection sheet \(\text{see Appendix A}\), and verified by an overseeing consultant who enters the data into the password-protected database.
CONFIDENTIALITY

Each patient is allocated a number on the database to maintain confidentiality, and the data are stored in a password-protected database only accessible to registered users. The hard copies of the capture forms are stored in a lockable cupboard accessible only to investigators.

INFORMED CONSENT

As the study was retrospective, informed consent was not required from the parents of participants.

ETHICS

The study was conducted according to the ethical guidelines and principles of the international Declaration of Helsinki, South African Guidelines for Good Clinical Practice and the Medical Research Council Ethical Guidelines for Research.

Ethical approval was granted by the Human Research Ethics Committee of the University Of Cape Town Faculty Of Health Sciences on 19 November 2014 (HREC Ref 853/2014). (See Appendix B)

DATA ANALYSIS

Data were captured manually using the VON data capture form, and entered into the VON database. Relevant parameters were documented in an Excel spreadsheet, and analysed using SPSS software.

Wilcoxon rank sum tests used to compare the distributions of GA and Weight between in- and out-born infants (skewed continuous valued variables) and chi-squared tests of association used to determine whether or not there was any association between birth location and various categorical variables. Significance was assessed at the 5% level
LIMITATIONS

As this was a retrospective study, we relied on data entered in patient records. In early 2012, before the staff was fully trained in record keeping for VON, some data were not always noted.

Gestational age is usually calculated based on sure dates of last menstrual period or early, first-trimester ultrasound. These are often not known in our setting, and gestational age estimates on late ultrasound or Ballard score are not always accurate. In addition, intrauterine growth restriction is relatively common in our setting of poor socioeconomic circumstances, substance abuse and maternal hypertension, but is poorly documented. Thus, analysis was only based on birth weight.

The literature describes 5 minute Apgar score as a marker of morbidity and mortality. Apgar scores in outborns are often not documented, or done at all when the patient is born outside of a health care facility. Resuscitation techniques and skills vary between facilities, and Apgar scoring can be inaccurate, so this variable was not included in the analysis.

As the Vermont Oxford Network is an international entity, locally relevant factors such as maternal HIV status and congenital infections are not routinely recorded.

Outborn neonates hail from many different locations, from being born at home, Level 1 clinics or in ambulances, to intensive care units at Level 2 hospitals. Many are suspected to demise before transport, with only the most robust making it to the Groote Schuur Nursery, but conversely only the sickest patients at Level 2 units are transferred across for specialist care, which may skew the perspective on these outcomes. Although the initial location of delivery plays a role in ultimate outcome, this was not explored within the scope of this study.

Outcomes data were devised using proxies of morbidity including: intraventricular haemorrhage, chronic lung disease, necrotising enterocolitis and late infection. Ideally our patients should all have long-term follow up to accurately assess neurodevelopmental outcomes, but in the context of this study it was not deemed viable.
DEFINITIONS OF PARAMETERS

All parameters are defined according to those of the VON database.

MATERNAL CHARACTERISTICS

Antenatal care

Antenatal care was defined as the mother having received any prenatal obstetric care prior to the admission during which delivery took place. This included care at Midwife Obstetric Units as well as secondary and tertiary level hospitals.

Antenatal steroids

In clinical practice, “steroid mature” refers to 2 doses of Betamethasone, given 12 hours apart, with the first dose at least 24 hours prior to delivery. The VON database considers any corticosteroids administered to the mother during pregnancy at any time prior to delivery as a positive finding.

Hypertension

This definition included chronic or pregnancy-induced hypertension, with a maternal systolic blood pressure over 140 or diastolic pressure over 90. The hypertension could be present with or without proteinuria and oedema, and included pre-eclampsia and eclampsia.

Chorioamnionitis

This finding was only positive if confirmed chorioamnionitis (usually on microscopy or histology of the placenta) was documented. This is often under-reported.

Caesarean section

Caesarean section deliveries, both elective and emergency, are only available at Level 2 and 3 institutions. In our referral area, Caesarean sections are only performed at Groote Schuur, Mowbray Maternity and New Somerset Hospital. Deliveries at MOU’s are all vaginal.
INFANT CHARACTERISTICS

Ventilatory support

Ventilatory support refers to invasive ventilation via endotracheal tube, and includes intermittent positive pressure ventilation (IPPV) and high frequency oscillatory ventilation (HFOV). Neonates over 800g are eligible for ventilation at the GSH Nursery. Clinically unstable neonates may be intubated and ventilated for ambulance transfer, accounting for part of the large number of ventilated outborns.

So-called in-out surfactant administration, where endotracheal intubation is undertaken only for the purpose of giving surfactant, is not regarded as intubation for ventilation. Multiple episodes of endotracheal intubation and duration of ventilation are also not accounted for in this data set.

Surfactant administration

The administration of exogenous (either porcine or bovine) surfactant via endotracheal tube at any time during admission was recorded. Multiple doses of surfactant were not measured.

Hypothermia on admission

Hypothermia on admission is regarded as a temperature of 35.9ºC or less recorded within the first hour of admission to the GSH Nursery.

OUTCOMES

Late infection

Late infection, which is usually regarded as nosocomial, is defined as a bacterial and/or fungal infection after day 3 of life. Only infections which were positive on blood culture were included.

Necrotising enterocolitis

Necrotizing enterocolitis is diagnosed using clinical and radiological signs. In order to fulfill criteria, the patients manifested with at least one clinical sign, including bilious gastric aspirates or emesis, abdominal distension and blood in the stool. Radiological criteria include pneumatosis intestinalis, hepato-biliary gas or pneumoperitoneum.
Severe intraventricular haemorrhage

Severe intraventricular haemorrhage (IVH) refers to neonates diagnoses with a grade 3 or 4 periventricular-intraventricular hemorrhage (PIH) on cranial ultrasound on or before day 28 of life, and is a risk for neurodevelopmental fallout in survivors.

Chronic lung disease

The definition of Chronic Lung Disease (CLD) was based on an algorithm used by the VON Database that was tested with hospital data and was found to be more accurate than Oxygen at 36 Weeks alone.

Survival with serious morbidity

Indicates whether the infant survived with none of the following key morbidities: Severe intraventricular haemorrhage, periventricular leukomalacia, chronic lung disease in patients <33 Weeks, necrotizing enterocolitis or any late infection.

Mortality

Mortality describes the patients who died at any time during their admission.
RESULTS

STUDY COHORT

A total of 1032 patients were enrolled.

906 (87.8%) were delivered at Groote Schuur Hospital, and 126 (12.2%) were outborn, having being delivered outside of Groote Schuur and requiring transport to our facility. Please see figure 1 for a breakdown of the location of delivery of the outborn cohort.

Location of delivery was predictive of both mortality and survival without morbidity (p <0.0001).

Figure 1: Location of delivery of outborns
MATERNAL CHARACTERISTICS

Antenatal Care

89.1% (807/906) of inborn mothers received antenatal care, compared with 57.9% (73/126) of outborn mothers (p <0.0001).

The provision of antenatal care was a statistically significant predictive factor for survival without morbidity (p <0.0001) and mortality (p 0.004).

Antenatal steroids

64.2% (582/906) of inborn and 15.2% (19/126) of outborn mothers received antenatal steroids (p <0.0001).

The provision of antenatal steroids was predictive for both survival without morbidity and mortality (p <0.0001).

Hypertension

54.6% (495/906) of mothers at Groote Schuur Hospital were treated for hypertension, compared with 3.2% (4/126) of mothers from other centres (p <0.0001). This finding is in keeping with the fact that hypertensive mothers in the Metro West area are referred for specialist care at Groote Schuur.

Chorioamnionitis

Data were missing for 39 patients (3.8% of the cohort)

Chorioamnionitis was reported in 6.4% (57/887) of inborns and 7.5% (8/106) of outborns. This was not statistically significant (p= 0.659).

Caesarean section

74.1% (671/906) of inborn deliveries were via Caesarean section, compared with 17.5% (22/126) of outborn deliveries (p <0.0001).
INFANT CHARACTERISTICS

Ventilatory support

Data were missing for 13 patients (1.3% of the cohort).

16.2% (143/893) of inborn neonates and 57.9% (73/126) of outborns were ventilated during their admission at Groote Schuur Hospital (p <0.0001).

Surfactant administration

25.3% (229/906) of inborns received surfactant, compared with 65.1% (73/126) of outborns (p <0.0001).

Hypothermia on admission

51 (4.9%) patients did not have documented temperatures within one hour of admission. Of the remaining patients, 44.4% (382/860) of inborns and 40.8% (49/120) of outborns were hypothermic on admission. This result was not statistically significant (p =0.465).

OUTCOMES

Late infection

No data were recorded for 94 (9.1%) patients.

Of the remaining cohort, 8.8% (73/827) of inborn and 23.4% (26/111) of outborn neonates developed culture-positive late infection (p <0.0001).

Necrotising enterocolitis

Data were not available for 14 (1.4%) patients.

5.9% of inborns (53/892) and 8.7% (11/126) of outborns developed NEC. The difference was not statistically significant (p= 0.227).
Severe intraventricular haemorrhage

140 patients (13.6%) did not have a cranial ultrasound in the first 28 days of life. Many demised before an ultrasound could be done, or were transferred to another facility before they were scanned.

Of those who did have an ultrasound, 3.7% of inborns (29/784) and 13.9% (15/109) of outborns were found to have severe intraventricular haemorrhage (p <0.0001).

Of the patients who survived to discharge, 2% of inborns and 6.3% of outborns had severe IVH (p = 0.039).

In the cohort who died, 17.2% of inborns and 35.7% of outborns who had cranial ultrasounds before their demise were found to have severe IVH (p = 0.02). These differences were not statistically significant.

Chronic lung disease

Data were missing on 200 (19.4%) patients, many of whom had likely not survived to 28 days or 36 weeks gestation.

Of the patients who survived to discharge, 5.3% (41/747) of inborns and 14.1% (12/85) of outborns developed chronic lung disease (p = 0.003).

Survival without morbidity

85% (628/739) of inborn and 70.2% (59/84) of outborn survivors did not have serious morbidity (p = 0.003). When broken down into weight categories (see Figure 2) increased weight was associated with increased survival without morbidity.

Access to antenatal care, antenatal steroids and inborn status were predictive for survival without morbidity (p <0.0001).

![Figure 2. Survival without morbidity of inborn vs outborn neonates at Groote Schuur Hospital](image)
Mortality

18.4% (167/906) of inborns and 33.3% (42/126) of outborns demised (p < 0.0001), mostly on the first 2 days of admission.

In the cohort weighing 800g and less, 53.6% of inborns and 87.5% of outborns demised. In patients weighing over 800g, the mortality of inborns and outborns was comparable, with a significant decrease in mortality with increasing birth weight (see Figure 3).

Predictors for mortality included antenatal steroids and birth location (p < 0.0001) as well as antenatal care (p = 0.004).

Figure 3. Mortality of inborn vs outborn neonates at Groote Schuur Hospital
**SUMMARY OF RESULTS**

Table 1: summary of results

<table>
<thead>
<tr>
<th></th>
<th>Inborn (%)</th>
<th>Outborn (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antenatal care</td>
<td>89.1</td>
<td>57.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Steroids</td>
<td>64.2</td>
<td>15.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>54.6</td>
<td>3.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Chorioamnionitis</td>
<td>6.4</td>
<td>7.5</td>
<td>0.659</td>
</tr>
<tr>
<td>Caesarean section</td>
<td>74.1</td>
<td>17.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ventilation</td>
<td>16.2</td>
<td>57.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Surfactant</td>
<td>25.3</td>
<td>65.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hypothermia</td>
<td>44.4</td>
<td>40.8</td>
<td>0.465</td>
</tr>
<tr>
<td>Late infection</td>
<td>8.8</td>
<td>23.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>NEC</td>
<td>5.9</td>
<td>8.7</td>
<td>0.227</td>
</tr>
<tr>
<td>Severe IVH</td>
<td>3.7</td>
<td>13.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>5.3</td>
<td>13.4</td>
<td>0.003</td>
</tr>
<tr>
<td>Survival without morbidity</td>
<td>85</td>
<td>70.2</td>
<td>0.003</td>
</tr>
<tr>
<td>Mortality</td>
<td>18.4</td>
<td>33.3</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
DISCUSSION

The concept of perinatal regionalisation was initially proposed in the USA in 1976, in the March of Dimes publication “Towards Improving the Outcome of Pregnancy”. It recommended that at-risk premature neonates be delivered in Level 3 hospitals with specialised perinatal services, and implementation of the model showed improvements in neonatal mortality rates throughout the USA \(^{31}\). Over the past few decades, the outcomes of Very- and Extremely Low Birth Weight neonates have improved significantly, particularly since the introduction on exogenous surfactant therapy in 1990 \(^{24}\) and the increased administration of antenatal steroids since the mid 1990’s \(^{18, 19}\). However, delivery outside of a Level 3 centre has remained a poor prognostic factor, largely as a result of less skilled resuscitation and initial care of premature neonates \(^{5}\) and the fact that outborn mothers were less likely to have received antenatal care and steroids \(^{14}\).

This study was conducted at a Level 3 centre in Cape Town, South Africa which admits over 500 premature neonates per year. As the designated Level 3 perinatal unit for the Metro West Health District, Groote Schuur Hospital’s obstetric team manages high-risk pregnancies, including those complicated by maternal hypertension. 75% of premature babies at Groote Schuur are delivered via caesarean section.

Previously, place of delivery was based on maternal condition, but since May 2012 the Groote Schuur nursery has adopted a policy of perinatal regionalisation, where at-risk premature neonates are to be transferred to our Level 3 service, preferably while still in-utero. Unfortunately, many deliveries still take place at Level 1 and 2 units, and the neonates subsequently transferred to the Groote Schuur Nursery for continued specialised care. Of the 1032 patients recruited to this study, 87.8% were born at Groote Schuur Hospital, and 12.2% were transferred in from other facilities.

In keeping with the literature, and reflecting the findings of South African case-controlled studies of preterm neonates born before arrival in Kwa-Zulu Natal \(^{32}\) and Johannesburg \(^{33}\), fewer outborn mothers received antenatal care. They were also less likely to receive timeous antenatal steroids, which play a significant role in improving lung maturity and thus decreasing the development of chronic lung disease, as well as being protective against intraventricular haemorrhage \(^{16}\). The consequences of not receiving antenatal steroids were evident in our cohort, with outborn neonates requiring more exogenous surfactant, and having an increased incidence of chronic lung disease and severe intraventricular haemorrhage compared with their inborn counterparts.
Neonates weighing 800g and above are eligible for invasive ventilatory support at the Groote Schuur Nursery. Clinically unstable neonates are often intubated by inexperienced staff and ventilated for ambulance transfer, accounting for part of the large number of ventilated outborns. Not only is intubation and ventilation difficult, risky and costly, it also increases the risk of hypotension and need for surfactant (another expensive procedure), as well as developing severe intraventricular haemorrhage and nosocomial sepsis. Inborn neonates admitted directly to the Groote Schuur Nursery have immediate access to non-invasive respiratory support, primarily CPAP, which is associated with less adverse events, decreased surfactant requirements and potentially a decreased incidence of chronic lung disease.

In a resource limited setting such as ours, it is particularly important that patients who survive do so with no morbidity, especially with regards to respiratory and neurodevelopmental outcomes. In comparison to the Canadian Neonatal Network database, our cohort had a higher rate of survival without morbidity (82% vs 37%), but at the cost of higher mortality (20% vs 10%) Access to antenatal care, antenatal steroids and inborn status were independent predictors for mortality and survival without morbidity.

An increased birth weight was associated with improved survival and outcomes, with outborns weighing over 800g having outcomes comparable with their inborn counterparts. In the group weighing 800g and less, however, inborns fared far better. 53.6% of inborns weighing less than 800g demised, compared with 87.5% of outborns. Of the two outborn patients weighing less than 800g who survived, only one did so without developing serious morbidity.

Most of the neonates who demised did so in the first 2 days of admission. When outborns are transferred to Level 3 care, they are often separated from their mothers, sometimes for several days. In the sub-800g group, this is particularly traumatic, as these neonates often demise before being reunited with their parents. Given the high cost of transport and therapy for these patients, the emotional burden on their families and their ultimate poor outcome, we recommend a revision of the current referral protocol. These neonates may benefit from remaining with their mothers; with specialist advice being provided telephonically to the centres caring for them, adequate counselling of their families, and a “comfort care” or palliative care approach being taken to ensure that these patients are treated with dignity during the hours or days they are alive.
CONCLUSION AND RECOMMENDATIONS

This study has demonstrated that perinatal regionalisation is beneficial to our patients, with timeous identification of at-risk pregnancies, administration of antenatal steroids and in-utero transfer to Level 3 care leading to excellent outcomes. Despite the referral protocol in place, many high-risk VLBW and ELBW deliveries still do not take place at Groote Schuur Hospital. We must continue to strive to strengthen regionalisation within the Metro West district in order to ensure that more premature neonates are delivered at appropriate facilities.

We also recommend allocation of resources to the training of midwives, ambulance staff and paramedics on resuscitation and early management of VLBW neonates who are delivered outside of Level 3 care to improve their ultimate outcomes.

We recommend a revision of the current Metro West referral protocol, with neonates weighing less than 800g being eligible for Level 3 care on a case by case basis. Given the high morbidity and mortality in this group, the emotional and financial costs of transfer are often not warranted. We suggest that they remain with their mothers at Level 1 and 2 facilities for the short duration of their lives, with an emphasis on comfort care. Those who are still clinically stable beyond the first day of life may be considered for transfer after discussion with a senior clinician at a Level 3 hospital. Training and support of staff at these facilities regarding management of extremely premature neonates, counselling of their families and provision of appropriate palliative care may prove extremely beneficial.
REFERENCES


APPENDIX A

VON data capture form

Center Number: ______________ Network ID Number: ______________

VERMONT OXFORD NETWORK
PATIENT DATA BOOKLET FOR INFANTS BORN IN 2013


Contents:
Page 1: Patient Identification Worksheet
Page 2: Length of Stay Calculation Worksheet
Page 3: 28 Day Form
Pages 4 & 5: Discharge Form (2 pages)
Page 6: Transfer and Readmission Form (only infants who transfer to another hospital)
Page 7: Supplemental Data Form (Expanded Database only)

PATIENT IDENTIFICATION WORKSHEET

W1. Patient’s Name: ________________________________

W2. Mother’s Name: ________________________________

W3. Patient’s Medical Record Number: ________________________________

W4. Date of Birth: ___/___/____

W5. Date of Admission: ___/___/____

For inborn infants, the date of admission is the Date of Birth.
For outborn infants, the date of admission is the date the infant was admitted to your hospital.

W6. Date of Day 28: ___/___/____

W7. Date of Week 36: ___/___/____

Use the Calculation Charts for Date of Day 28 and Date of Week 36 for the infant’s birth year.

W8. Date of Initial Disposition: ___/___/____

W9. If Infant Transferred, Date Discharged Home, Died or First Birthday (if still hospitalized), whichever is Soonest: ___/___/____

DO NOT SUBMIT THIS WORKSHEET
Protected Health Care Information

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LENGTH OF STAY CALCULATION WORKSHEET
FOR INFANTS BORN IN 2013

Protected Health Care Information. DO NOT SUBMIT this Worksheet to Vermont Oxford Network.

Use items W5, W8 and W9 from the Patient Identification Worksheet when completing this form.

Find the day numbers corresponding to dates using the Day Number Chart for 2013-2014 (www.vtoxford.org).

Part A. Initial Length Of Stay

Enter Date of Initial Discharge, Transfer or Death (W8): ______/____/____  □□□□ Day #
Subtract Date of Admission to Your Hospital (W5): ______/____/____  □□□□ Day #
For inborn infants, the date of admission is the Date of Birth.
For outborn infants, the date of admission is the date the infant was admitted to your hospital.
Add 1:
L1. INITIAL LENGTH OF STAY = □□□□ Days

Note: the maximum value of Initial Length of Stay is 366 (or 367 if leap day must be added), because tracking ends on the infant’s first birthday.

Part B. Total Length Of Stay

Only For Infants Transferred From Your Hospital to Another Hospital.

Enter Date of Final Discharge or Death (W9): ______/____/____  □□□□ Day #
Subtract Date of Admission (W5): ______/____/____  □□□□ Day #
For inborn infants, the date of admission is the Date of Birth.
For outborn infants, the date of admission is the date the infant was admitted to your hospital.
Add 1:
L2. TOTAL LENGTH OF STAY = □□□□ Days

Note: the maximum value of Total Length of Stay is 366 (or 367 if leap day must be added), because tracking ends on the infant’s first birthday.

SAMPLE CALCULATION OF INITIAL LENGTH OF STAY

Enter Date of Initial Discharge, Transfer or Death: 02 / 26 / 2013  □□□□ Day #
Subtract Date of Admission: 01 / 13 / 2013  □□□□ Day #
Add 1:
L1. INITIAL LENGTH OF STAY = □□□□ Days

Explanation: Date of 02/26/2013 is Day Number 57. Date of 01/13/2013 is Day Number 13. The day numbers for each date are found in the 2013-2014 Day Number Chart on the Network web site, www.vtoxford.org.

PLEASE DO NOT SUBMIT THIS WORKSHEET
Protected Health Care Information
28 DAY FORM - For Infants Born in 2013

Center Number: _______ Network ID Number: _______ Year of Birth: _______

1. Birth Weight: _______ grams

2. Gestational Age:  
a) Weeks _______  
b) Days (0-6) _______

3. Died in Delivery Room:  
   □ Yes  
   □ No  
   (If Yes, Use Delivery Room Death Form.)

4. a) Location of Birth:  
   □ Inborn  
   □ Outborn
   b) If Outborn, Day of Admission to Your Center (Range: 1 to 28. Date of Birth is Day 1): _______
   c) If Outborn, Transfer Code of Center from which Infant Transferred: _______
   (List available at http://www.vtoxford.org/transfers)

5. Head Circumference at Birth (in cm to nearest 10th): _______

6. Maternal Ethnicity/Race (Answer both a and b):  
a) Ethnicity of Mother:  
   □ Hispanic  
   □ Not Hispanic
   b) Race of Mother:  
   □ Black or African American  
   □ White  
   □ Asian  
   □ American Indian or Alaska Native  
   □ Native Hawaiian or Other Pacific Islander  
   □ Other

7. Prenatal Care:  
   □ Yes  
   □ No

8. Antenatal Steroids:  
   □ Yes  
   □ No

9. Antenatal Magnesium Sulfate:  
   □ Yes  
   □ No

10. Chorioamnionitis:  
    □ Yes  
    □ No

11. Maternal Hypertension, Chronic or Pregnancy-Induced:  
    □ Yes  
    □ No

12. Mode of Delivery:  
    □ Vaginal  
    □ Cesarean Section

13. Sex of Infant:  
    □ Male  
    □ Female

14. a) Multiple Gestation:  
    □ Yes  
    □ No  
    b) If Yes, Number of Infants Delivered: _______

15. APGAR Scores:  
    a) 1 minute _______  
    b) 5 minutes _______

16. Initial Resuscitation:  
a) Oxygen:  
   □ Yes  
   □ No
   b) Face Mask Vent:  
   □ Yes  
   □ No
   c) Endotracheal Tube Vent:  
   □ Yes  
   □ No
   d) Epinephrine:  
   □ Yes  
   □ No
   e) Cardiac Compression:  
   □ Yes  
   □ No
   f) Nasal CPAP  
   □ Yes  
   □ No

17. a) Temperature Measured within the First Hour after Admission to Your NICU:  
    □ Yes  
    □ No  
    □ N/A
   b) If Yes, Temperature Within the First Hour after Admission to Your NICU  
   (in degrees centigrade to nearest 10th): _______

18. Bacterial Sepsis on or before Day 3:  
   □ Yes  
   □ No

19. Oxygen on Day 28:  
   □ Yes  
   □ No  
   □ N/A (See Manual for N/A criteria)

20. Periventricular-Intraventricular Hemorrhage (PIH):  
a) Cranial Imaging (US/CT/MRI) on or before Day 28:  
   □ Yes  
   □ No
   b) If Yes, Worst Grade of PIH (0-4):  
   _______
   c) If PIH Grade 1-4, Where PIH First Occurred:  
   □ Your Hospital  
   □ Other Hospital  
   □ N/A

21. Died Within 12 Hours of Admission to Your NICU:  
    □ Yes  
    □ No
22. **Respiratory Support** (at any time after leaving the delivery room/initial resuscitation area):
   a) Oxygen after Initial Resuscitation: □ Yes □ No
   b) Conventional Ventilation after Initial Resuscitation: □ Yes □ No
   c) High Frequency Ventilation after Initial Resuscitation: □ Yes □ No
   d) High Flow Nasal Cannula after Initial Resuscitation: □ Yes □ No
   e) Nasal IMV or Nasal SIMV after Initial Resuscitation: □ Yes □ No

23. a) Nasal CPAP after Initial Resuscitation: □ Yes □ No
    b) NCPAP before or without ever having received ETT Vent: □ Yes □ No □ N/A

24. a) Surfactant during Initial Resuscitation: □ Yes □ No
    b) Surfactant at Any Time: □ Yes □ No (Item 24.b must be Yes if Item 24.a is Yes)
       c) Age at First Dose: □ Yes □ No (Item 24.c must be Yes if Item 24.a is Yes)
       d) Minutes (0-59) __________

25. a) Inhaled Nitric Oxide: □ Yes □ No
    b) If Yes, where given: □ Your Hospital □ Other Hospital □ Both

26. **Respiratory Support at 36 Weeks** (See Manual for N/A criteria):
   a) Oxygen at 36 Weeks: □ Yes □ No □ N/A
   b) Conventional Ventilation at 36 Weeks: □ Yes □ No □ N/A
   c) High Frequency Ventilation at 36 Weeks: □ Yes □ No □ N/A
   d) High Flow Nasal Cannula at 36 Weeks: □ Yes □ No □ N/A
   e) Nasal IMV or SIMV at 36 Weeks: □ Yes □ No □ N/A
   f) Nasal CPAP at 36 Weeks: □ Yes □ No □ N/A

27. a) Steroids for CLD: □ Yes □ No
    b) If Yes, Where Given: □ Your Hospital □ Other Hospital □ Both

28. Indomethacin for Any Reason: □ Yes □ No

29. Ibuprofen for PDA: □ Yes □ No

30. Probiotics: □ Yes □ No

31. Treatment of ROP with Anti-VEGF Drug: □ Yes □ No

32. a) ROP Surgery: □ Yes □ No
    b) If Yes, Where Done: □ Your Hospital □ Other Hospital □ Both

33. a) PDA Ligation: □ Yes □ No
    b) If Yes, Where Done: □ Your Hospital □ Other Hospital □ Both

34. Surgery for NEC, Suspected NEC, or Bowel Perforation: □ Yes □ No
   (If Yes, a Surgery Code is Required in Item 36a)

35. Other Surgery: □ Yes □ No
   (If Yes, a Surgery Code is Required in Item 36a)

36a. **If Yes to NEC Surgery or Other Surgery, Surgical Codes** (See Appendix D): If NEC Surgery, one or more of the following codes is required: S302, S303, S307, S308, S309, S333. Indicate location of surgery for each surgery code.

   Surgery Code 1: __________ □ Your Hospital □ Other Hospital □ Both
   Surgery Code 2: __________ □ Your Hospital □ Other Hospital □ Both
   Surgery Code 3: __________ □ Your Hospital □ Other Hospital □ Both
   Surgery Code 4: __________ □ Your Hospital □ Other Hospital □ Both
   Surgery Code 5: __________ □ Your Hospital □ Other Hospital □ Both
   Surgery Code 6: __________ □ Your Hospital □ Other Hospital □ Both
   Surgery Code 7: __________ □ Your Hospital □ Other Hospital □ Both
   Surgery Code 8: __________ □ Your Hospital □ Other Hospital □ Both
   Surgery Code 9: __________ □ Your Hospital □ Other Hospital □ Both
   Surgery Code 10: __________ □ Your Hospital □ Other Hospital □ Both

36b. Include description for codes S100, S200, S300, S400, S500, S600, S700, S800, S900, S1000 & S1001:
**DISCHARGE FORM - For Infants Born in 2013**

**PAGE 2**

Center Number: _______ Network ID Number: _______ Year of Birth: _______

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>37. Respiratory Distress Syndrome:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>38. a) Pneumothorax:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>b) If Yes, Where Occurred:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>39. Patent Ductus Arteriosus:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40. a) Necrotizing Enterocolitis:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>b) If Yes, Where Occurred:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>41. a) Gastrointestinal Perforation:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>b) If Yes, Where Occurred:</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Sepsis and/or Meningitis, Late (after day 3 of life):** *(See Manual for N/A criteria)*

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>42. a) Bacterial Pathogen:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b) If Yes, Where Occurred:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>43. a) Coagulase Negative Staph:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b) If Yes, Where Occurred:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>44. a) Fungal Infection:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b) If Yes, Where Occurred:</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

45. Cystic Periventricular Leukomalacia:                                  |     |    |     |

46. ROP:  
   a) Retinal Exam Done:                                                |     |    |     |
   b) If Yes, Worst Stage of ROP (0-5):                                    |     |    |     |

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>47. Major Birth Defect:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If Yes, enter codes:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Include description for Codes 100, 504, 601, 605, 901, 902, 903, 904 &amp; 907:</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Question</th>
</tr>
</thead>
<tbody>
<tr>
<td>48. Enteral Feeding at Discharge:</td>
</tr>
<tr>
<td>None</td>
</tr>
<tr>
<td>Human Milk Only</td>
</tr>
<tr>
<td>Formula Only</td>
</tr>
<tr>
<td>Human milk in combination with either fortifier or formula</td>
</tr>
</tbody>
</table>

49. Oxygen and Monitor at Discharge:                                     
   a) Oxygen at Discharge:                                               |     |    |
   b) Monitor at Discharge:                                              |     |    |

50. Initial Disposition (check only one):                                 
   a) Home                                                                 |
   b) Died                                                                 |
   c) Transferred to another Hospital  
      (★ Complete Transfer and Readmission Form)                        |
   d) Still Hospitalized as of First Birthday                            |

<table>
<thead>
<tr>
<th>Question</th>
</tr>
</thead>
<tbody>
<tr>
<td>51. Weight at Initial Disposition:</td>
</tr>
<tr>
<td>grams</td>
</tr>
</tbody>
</table>

52. Head Circumference at Initial Disposition (in cm to the nearest 10th):|

53. Initial Length of Stay:                                               |
   (Item L1 on Length of Stay Calculation Worksheet)                       |
TRANSFER & READMISSION FORM - For Infants Born in 2013

Center Number: _______  Network ID Number:  □□□□□□□□ Year of Birth: ______

Part A. Complete for ALL Transferred Infants

If an infant is transferred to another hospital, complete Items 54 - 56. Post Transfer Disposition (Item 56) refers to the infant’s disposition upon leaving the “transferred to” hospital.

54. Reason for Transfer: (Check Only One)
   □ Growth/Discharge Planning  □ Medical/Diagnostic Services
   □ Surgery  □ ECMO  □ Chronic Care  □ Other

55. Transfer Code of Center to which Infant Transferred: ________ (List available at http://www.vtoxford.org/transfers)

56. Post Transfer Disposition (check only one):
   □ Home
   □ Transferred Again to Another Hospital (2nd Transfer)
   □ Died
   □ Readmitted to Any Location in Your Hospital
   □ Still Hospitalized as of First Birthday

Part B. Complete ONLY for Readmitted Infants

If a patient is readmitted to your center after transferring once to another hospital without having been home, answer Items 57 - 58. When infants are readmitted to your center, continue to update Items 18 - 20 on the 28 Day Form, and Items 22 - 49 on the Discharge Form based on all events at both hospitals until the date of Disposition after Readmission. If your hospital participates in the Expanded Database and definition criteria are met, update Items S1.B, S1.C.1, S1.C.2, S2.A.1, S2.A.2 and S2.C based on events that occur following transfer and readmission.

57. Disposition after Readmission (check only one):
   □ Home
   □ Died
   □ Transferred Again to Another Hospital
   □ Still Hospitalized as of First Birthday

58. Weight at Disposition after Readmission: ________ grams

Part C. Complete ONLY for Infants Who Transferred More Than Once

Answer Item 59 if an infant transferred from your center to another hospital and was then either (1) transferred again to another hospital, or (2) readmitted to your center and then transferred again to another hospital.

59. Ultimate Disposition (check only one):
   □ Home  □ Died  □ Still Hospitalized as of First Birthday

Part D. Complete for ALL Transferred Infants

Complete Item 60 when the infant has been discharged Home, Died or is Still Hospitalized as of First Birthday, whichever comes first.

60. Total Length of Stay: ________ day(s)  (Item 2 on Length of Stay Calculation Worksheet)
**SUPPLEMENTAL DATA FORM - For Infants Born in 2013**
(For Expanded Database Centers)

Center Number: ______  Network ID Number: ______  Year of Birth: ______

### S1. Treatments:

- **A. 1. Duration of Assisted Ventilation:**
  - [] None
  - [] <4 hours
  - [] 4-24 hours
  - [] > 24 hours
  - [] N/A
  - **2. If > 24 hours, Total Days of Assisted Ventilation:** ______

- **B. ECMO at your Hospital:**
  - [] Yes
  - [] No
  - [] N/A

- **C. Hypothermic Therapy at Your Hospital:**
  - 1. **Was Hypothermic Therapy Performed at Your Hospital:**
    - [] Yes
    - [] No
  - 2. **If Yes, Cooling Method:**
    - [] Selective Head
    - [] Whole Body
    - [] Both

### S2. Diagnoses:

- **A. 1. Hypoxic-Ischemic Encephalopathy:**
  - [] Yes
  - [] No
  - [] N/A
  - **2. HIE Severity (check one):**
    - [] Mild
    - [] Moderate
    - [] Severe
    - [] N/A

- **B. 1. Meconium Aspiration:**
  - [] Yes
  - [] No

- **2. Tracheal Suction for Meconium Attempted in the DR:**
  - [] Yes
  - [] No
  - [] N/A

- **C. Seizures:**
  - [] Yes
  - [] No
  - [] N/A
APPENDIX B

Ethics Approval

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room 852-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 404 7662 • Facsimile [021] 406 6411
Email: research@uct.ac.za
Website: www.health.uct.ac.za/research/humanethics/forms

19 November 2014

HREC REF: 853/2014

Prof M Harrison
Department of Neonatology
GSH

Dear Prof Harrison

PROJECT TITLE: SHORT-TERM OUTCOMES OF INBORN VS OUTBORN VERY LOW BIRTHWEIGHT NEONATES (<1500G) IN THE GROOTE SCHUUR NEONATAL NURSERY. (MMed candidate- Dr L Gibbs)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee for review.

It is a pleasure to inform you that the HREC has formally approved the above-mentioned study.

Approval is granted for one year until the 30th November 2015.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure Form if the study is completed within the approval period.

(Forms can be found on our website: www.health.uct.ac.za/research/humanethics/forms)

We also acknowledge that MMed student Dr Lyndal Gibbs is involved in the study.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the HREC reference no in all your correspondence.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN ETHICS
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001936

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP) and Declaration of Helsinki guidelines.

The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.